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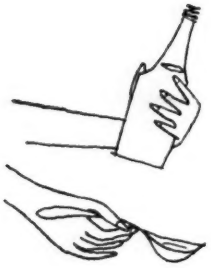

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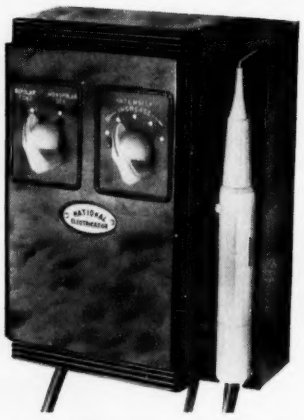

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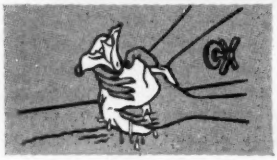

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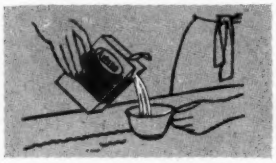

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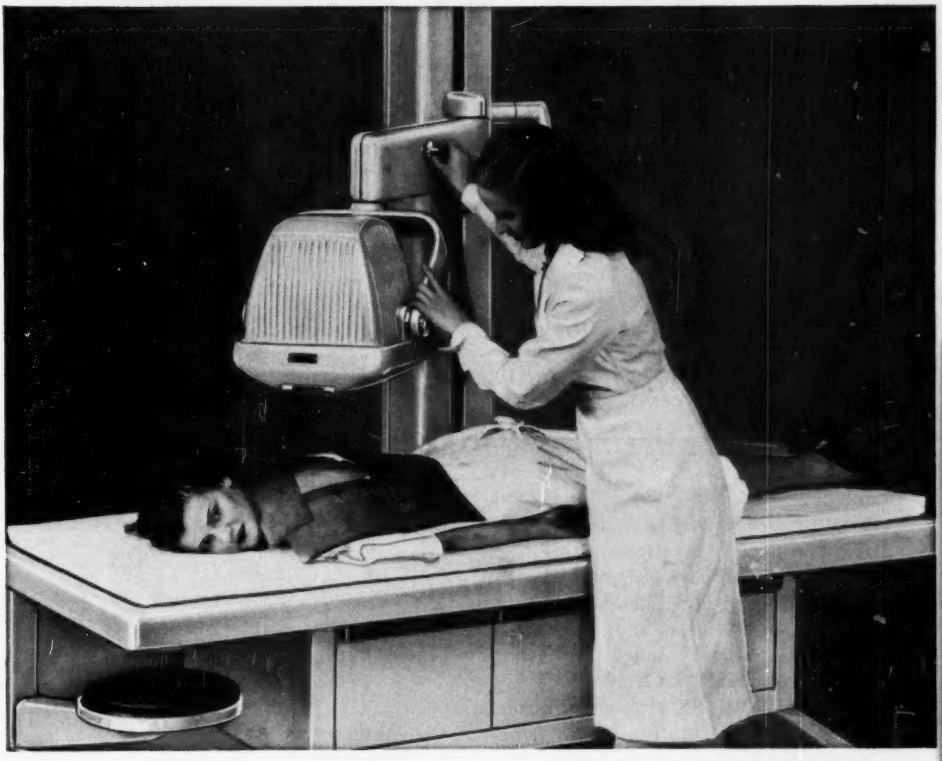

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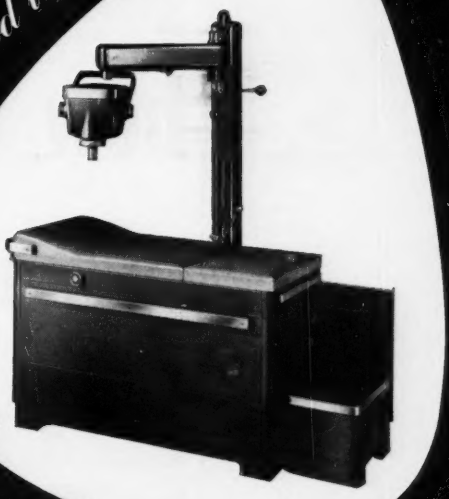

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A. M. A.
Archives of Dermatology and Syphilology

VOLUME 63 JANUARY 1951 NUMBER 1

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ACTUAL CAUSES OF CERTAIN OCCUPATIONAL DERMATOSES

III. A Further Study with Special Reference to Effect of Alkali on the Skin, Effect of Soap on p_H of Skin, Modern Cutaneous Detergents

JOSEPH V. KLAUDER, M.D.
AND
BENJAMIN A. GROSS, M.D.
PHILADELPHIA

IN PREVIOUS reports [1] study was made of cutaneous diseases in patients observed by us who presented claims for compensation under the Pennsylvania law.

In these studies we classified actual causes into groups rather than emphasizing occupation in relation to cause or making the simplest of classifications, namely, division of responsible agents into chemical, physical and biologic ones. We believe it is preferable to emphasize actual causes, since attention is focused on these causes. Prevention and investigative measures are suggested, and teaching of the subject is facilitated.[2]

The cases previously reported total 2,297; of the patients 1,729 were male and 568 female. The diseases of 1,059 (46.1 per cent) were diagnosed as occupational in origin and those of 1,238 as nonoccupational.

The nonoccupational group was comprised of a variety of diseases of the skin. Diagnosis of the cutaneous lesion is the initial requirement in differentiating occupational from nonoccupational cause. This fact serves to emphasize that valid opinion of the causes necessitates qualification in dermatological diagnosis.

Diagnosis of the occupational group was made after a thorough history taking, a complete physical examination and the acquisition of complete knowledge of the nature of the work and substances to which

From the Research Institute for Cutaneous Diseases, now the Institute of Public Health and Preventive Medicine, Temple University, Dr. John A. Kolmer, director.

1. (*a*) Klauder, J. V.: Actual Causes of Certain Occupational Dermatoses, Arch. Dermat. & Syph. **48**:579-600 (Dec.) 1943. (*b*) Klauder, J. V., and Hardy, M. K.: Actual Causes of Certain Occupational Dermatoses: II, Occup. Med. **1**:168-181 (Feb.) 1946.

2. Klauder, J. V.: Teaching of Occupational Dermatoses, Arch. Dermat. & Syph. **48**:153-158 (Aug.) 1943.

the claimant was exposed. When necessary, information was obtained from an employment source and from the manufacturer of the substance suspected of causing the dermatosis.

We herewith report an additional 1,412 cases of cutaneous diseases in patients observed by us who presented claims under the Pennsylvania law. The diseases of 614 (43.4 per cent) were diagnosed as occupational in origin and those of 798 as nonoccupational.

The cases previously reported and those now reported total 3,709; 2,850 of the patients were male, and 859 were female. The diseases of 1,673 (45.08 per cent) were diagnosed as occupational in origin and those of 2,036 as nonoccupational.

The actual causes of the occupational dermatoses of the 1,673 are classified in the following groups:

	No. of Cases	Per Cent
Primary irritants (acids, alkalis, solvents [nonaqueous])	479	28.6
Trauma and accidental injury	378	22.6
Sensitizing substances	228	13.6
Wet work (water alone, soap and water and alkaline salt detergents)	219	13.1
Cleansing agents applied to the skin	179	10.7
Petroleum products and other causes (hydrochlorinated hydrocarbons, vegetable oil, dust) of folliculitis	154	9.2
Physical and biologic agents	36	2.2

PRIMARY IRRITANTS

Primary irritants were the chief cause of occupational dermatoses in the entire series of 1,673 cases. In the previous studies [1] the role of acids, alkalis and nonaqueous solvents was discussed in relation to occupation. It will now suffice to summarize the following important substances embraced in the category of primary irritants: chromic acid and chromates, sulfuric acid, oxalic acid, zinc chloride, calcium chloride, tar, pitch, creosote, cresol(s), cupric sulfate, sodium sulfide, pine oil, sulfur dioxide, formaldehyde, pickling (processing of food) and dyeing solutions, insecticides, paints, enamels and varnishes. Among chemists the following were causal irritants: monochloroacetic acid, some ammonium compounds and bromofluorene.

Of the alkalis the following were most frequently found to be primary irritants: cyanides, sodium hydroxide, calcium oxide, cement, silicates and diluted ammonia solution.

Nonaqueous solvents were the predominating causal irritants in previous studies. Their role is again emphasized in the 614 additional cases now reported. Among the 614 cases there were 171 instances of dermatoses caused by primary irritants, of which 68 were attributed to

acids and alkalis and 103 to solvents. Kerosene, gasoline, turpentine and paint thinner were the most frequent offenders, although as many as 15 different solvents were represented as causing dermatitis.

The role of solvents in causation of occupational dermatitis was especially discussed in a previous publication.[1b] The following circumstances were most frequent in causing dermatitis of the hands: the use of a solvent as an anticorrosion oil on such parts (handled by the worker) as ball bearings and pistons; its use as a cutting oil or as an additive substance to cutting oil; the use of a solvent (usually kerosene) to clean the article of work or small mechanical parts, in this process the part being immersed by hand into a solvent without the use of gloves (fig. 1), machinists, machine operators and a variety of other workers being

Fig. 1.—Dermatitis caused by kerosene. The patient cleaned tools and small machine parts in a bucket of kerosene. He immersed his ungloved hand and forearm into the kerosene. In addition he used this solvent as a hand cleanser about six times daily. The dermatitis disappeared about one month after his cessation of this work.

affected, and the cleaning of large objects, notably printing presses, with a cloth saturated with a solvent, the cloth invariably being immersed by hand into the solvent.

Solvents play an additional role in causing occupational dermatoses through their use as hand cleansers. This aspect is classified under the heading of cleansing agents applied to the skin and is later discussed.

Klauder and Brill [3] studied the irritant action on the skin of petroleum fractions between kerosene and light spindle oil. They concluded that

3. Klauder, J. V., and Brill, F. A., Jr.: Correlation of the Boiling Ranges of Some Petroleum Solvents with Their Irritant Action on the Skin, Arch. Dermat & Syph. **56**:197-212 (Aug.) 1947.

kerosene of naphthenic origin was a greater irritant than one of paraffinic origin; kerosene and solvents of lower boiling range uniformly exerted irritant action.

Irritant action became less (qualitatively as well as quantitatively) at about the end boiling range of kerosene and progressively decreased as the boiling range increased, reaching a minimum at the boiling range of light spindle oil. Irritant action was therefore in direct ratio to the boiling range. In contrast, defatting action is in inverse ratio to the boiling range.

TRAUMA AND ACCIDENTAL INJURY

Trauma and accidental injury constituted the second most frequent cause, direct or indirect, of occupational dermatoses. Dermatitis resulting from the splash of a caustic or hot solution was placed in this category rather than in the category of lesions caused by primary irritants. All untoward cutaneous reactions and all infections resulting from accident and injury were likewise included in this group rather than classified under the heading of dermatoses with physical or biologic causes—for example, alopecia areata, herpes zoster, anthrax, erysipeloid, sporotrichosis and local as well as systemic reactions to medicaments used in treatment of an injury. Such responsible medicaments included antibiotics, sulfanilamide compounds, tetanus antitoxin, butacaine (butyn®) sulfate, butamben (butesin®) picrate, tincture mercocresols (mercresin®), oxyquinoline, nitrofurazone (furacin®) and foille® ointment (an antiseptic ointment of complex composition containing ethyl aminobenzoate).

Conspicuous in this category was eczematous dermatitis caused by an occlusive dressing, discharge or adhesive plaster or initiated by a wound or burn or from overtreatment.

The following unusual untoward reactions to injury were observed in the 614 additional cases now reported.

An automobile mechanic slipped while lifting an engine from the floor; the left knee struck the floor, and the right leg was forcibly abducted. He experienced pain in the region of Poupart's ligament and also soreness; the latter persisted. An eruption of herpes zoster affecting the right side appeared 30 hours later. In consideration of the relation of herpes zoster to injury, at times trivial and indirect, as after osteopathic manipulation, as reported elsewhere,[4] we regarded the herpes zoster of this patient as having an occupational relation.

A welder experienced conjunctivitis ("flash burn") of both eyes attributed to the ultraviolet radiation in the welding arc. Inflammation of the left eye disappeared in a few days. That of the right eye persisted

4. Klauder, J. V.: Herpes Zoster Appearing After Trauma, J. A. M. A. **134:** 245-248 (May 17) 1947.

with increasing severity. Two weeks later interstitial keratitis of congenital syphilis was diagnosed. This case conformed with others of interstitial keratitis following injury reported by one of us.[5]

The many and varied cutaneous reactions as sequelae of accident and injury, totaling as many as 18 different diseases of the skin, were discussed in previous publications [1] and need not be discussed further.

Doubtless by reason of the previously mentioned methods of classification, accident and injury as a cause of occupational dermatoses has not been stressed by other writers and has not received the attention we believe it merits. Accidental injury occurring in the course of employment represents the most frequent reason for compensation in the United States.[2] The next most frequent reason is occupational dermatoses. Our previous study emphasized safety appliances and means of preventing accidents in prevention of occupational dermatoses.

SUBSTANCES CAUSING SENSITIZATION DERMATITIS

In previous publications the substances causing sensitization dermatitis of patients reported with occupational dermatoses from this source were enumerated. In our present series of 614 cases of occupational dermatoses there were 73 instances of sensitization dermatitis.

As in previous studies phenol-formaldehyde resin (bakelite®) was the most frequent cause (17 of the 73 cases). The next most frequent cause was Rhus (13 cases). Sensitization dermatitis caused by a phenol-formaldehyde resin occurred not only among employees engaged in the manufacturing of laminated bakelite® products but also among workers handling the resin as a glue (carpenters, woodworkers and cabinetmakers) and as an insulating and heat resisting agent.

In the food-processing industry sensitization dermatitis was observed as follows: in a woman who prepared mushrooms for use in canned soup and from cinnamon handled by bakers (fig. 2).

A worker who weighed nickel phosphate for use in electroplating solutions became sensitized to nickel. A glazier became sensitized to putty which was said to contain a substitute for linseed oil. A solution called collo® gum (according to the manufacturers, the American Gum and Liquid Glue Company, comprised of potato starch treated with an alkali and neutralized with an acid, with 0.5 per cent phenol and formaldehyde) caused dermatitis in a man engaged in applying it on straw hats.

Oil used on yarn and wool caused dermatitis among employees of several different textile mills. Information concerning the formula of these oils could be obtained only in the case of one; of the ingredients

5. Klauder, J. V.: Ocular Syphilis: IV. Interstitial Keratitis and Trauma, Arch. Ophth. **10**:302-328 (Sept.) 1933.

suspected as allergenic were wood rosin and peanut oil. Oil used on yarn and wool throughout the textile industry is apparently rarely the cause of sensitization dermatitis. Such dermatitis in textile workers from "sulfonated oils" was reported by Osborne and Putnam [6] and by Schwartz.[7] In neither instance, however, was the type of sulfonated oil or the additives determined.

Women engaged in making cigars became sensitized to the wrapper of cigars. Patch test study suggested the insecticide sprayed on the growing leaf rather than tobacco itself as the sensitizer. As previously reported we observed sensitization to the paste employed on the wrapper of cigars. Sensitization to tobacco leaf is apparently rare.

Fig. 2.—Sensitization dermatitis caused by cinnamon. The patient was a baker and sprinkled cinnamon held in his hand. Patch testing with cinnamon elicited a positive reaction.

A roofer experienced acute dermatitis of the face and neck each time he was exposed to the fumes of certain pitches [8] (fig. 3).

Newcomers among the many substances to which workers may become sensitized are streptomycin and penicillin. Sensitization derma-

6. Osborne, E., and Putnam, E. D.: Industrial Dermatoses, with Special Reference to Allergy and Mycotic Dermatitis, J. A. M. A. **99**:972-977 (Sept. 17) 1932.

7. Schwartz, L.: Actual Causes of Dermatitis Attributed to Socks, Pub. Health Rep. **49**:1176-1185 (Oct. 5) 1934.

8. A discussion of dermatoses due to tar and pitch is given in Jenkins, W.: Dermatoses Among Gas and Tar Workers, Bristol, England, John Wright & Sons, Ltd., 1948. Acute erythema of face, neck, hands and forearms after exposure to vapor of tar and pitch is called by pitch workers "the smarts."

titis occurred in employees of pharmaceutical manufacturers engaged in filling vials with these antibiotics and in making penicillin tablets. The latter work entails exposure to powdered penicillin. The following clinical pattern was observed. The face and neck were more affected than the forearms, and the hands were least affected. The eruption was

Fig. 3.—Acute dermatitis of the face and neck of a roofer, which appeared before he applied pitch to a roof. He had had frequent attacks of redness and smarting of the face after exposure to fumes only of some pitches.

not acute and was comprised of erythematous scaly lesions which on the face and ears resembled seborrheic dermatitis. The reaction to a patch test with powdered penicillin was positive.

Dermatitis was observed from rubber gloves, the rubber band of a mask, a chemical use for mildew-proofing; perana pine (Araucaria

brasiliana) and Honduras pine (in a cabinet maker) and the insulating cover of a wire. Chemists became sensitized to the following compounds: phthalic maleic anhydride, chloromaleic anhydride, parachlorobenzyl chloride, 1-nitroso-2-naphthol and ethyldenediamine. With the two latter compounds clinical evidence suggested allergenic rather than primary irritant action. The dermatitis was too pronounced to warrant patch test study to determine the answer with certainty.

As discussed in previous publications mineral oil has a low allergenic index. Sensitization dermatitis from cutting oils, slushing oils and rust-proofing compounds is more reasonably ascribed to the additives. Workers were observed with sensitization dermatitis caused by an anticorrosion grease called andox® B, and another worker showed a condition due to cutting oil. Patch tests gave positive reactions to these substances, whereas such tests with petrolatum and with petroleum oils of high boiling range gave negative reactions. Manufacturers are not inclined to disclose the nature of additives in cutting oil and in anticorrosion compounds. Sellei and Leiber [9] compiled listings of eight classes comprised of 39 different compounds of varied nature that are used as additives.

WET WORK

In the 614 additional cases of occupational dermatoses there were 108 instances of dermatitis attributed to wet work. The category of dermatitis caused by wet work includes an eczematous dermatitis of the hands, in some instances of the forearms, in workers whose work was such that the hands and at times the forearms were wet with an aqueous solution most of or the entire work day. Such work concerned handling an object of work which was processed in the wet state (skins, hides, yarn and felt hats, for example) or which in its natural state was wet (the opening of oysters) or was cleansed or immersed in a solution.

Since water is essential in most industries, the classification of those with dermatitis caused by wet work covers persons in a wide range of occupations. The most numerous were those employed in the textile trades, tanneries, dye houses and abattoirs and in work concerned with the processing, preparation of and sale of food and beverages. In the latter category kitchen, restaurant and lunch counter workers were well represented.

Included were workers exposed to soap and water, soap powder and other cleansing compounds containing alkaline salt detergents. These were barbers, beauty parlor operators, dish, pot, pan, bottle and glass washers, soda fountain and lunch counter clerks, porters, janitors, scrub-

9. Sellei, H., and Leiber, E.: Chemical and Physical Mechanism of Engine Preservation Oil, Lubrication Eng. **3**:16-23 (Sept.) 1947.

women and other workers who cleanse a variety of objects. In these workers an additional cause of occupational dermatitis is the effect, as will be discussed, of prolonged exposure to alkali.

CLEANSING AGENTS APPLIED TO THE SKIN

Among the 614 additional persons with occupational dermatoses there were 69 whose dermatitis of the hands was attributed to the method of hand cleansing. Volatile solvents were employed by 44; chemic (a mixture of sodium carbonate and calcium hypochlorite) or sodium hypochlorite was used by 8, and excessive handwashing with soap was incriminated in the condition of 17.

It is apparent that volatile solvents constituted the predominating cause of dermatitis attributed to hand cleansing in the cases now reported as well as in the entire series (179 cases) reported under this category. Among the 44 patients of the present group the most frequently encountered occupational groups were painters (13 cases), including workers who temporarily performed a painting job, who frequently used turpentine or paint thinner, and machinists (9 cases), who commonly used kerosene or gasoline. A variety of other occupations, in which workers removed such material as ink, tar, glue, gum, cement (used as a cohesive) and other mucilaginous and viscous substances, grease and oily material, stain, lacquer and varnish, were represented. Newcomers among the many employed solvents were Diesel fuel oils (their boiling ranges are a little above that of kerosene, more comparable to that of mineral seal oil [3]) employed by workers in railroad repair shops and by men engaged in servicing and repairing Diesel motors of buses.

Chemic was employed by workers in dyehouses and tanneries and employees of manufacturers of coloring material. Its harmful effect was attributed to its alkalinity, its use in amounts more than required to remove dye or stain and the employees' failure to use a buffer solution after its use. For this purpose White [10] advised immersion of the hands in a solution of sodium bisulfite ($NaHSO_3$).

Excessive washing of the hands with soap, as much as 25 times a day, was performed by bakers, food handlers and others of whom clean hands are required for handling of the object of work or the writing of records.

Our study emphasizes the need of educating and instructing workers as to proper methods of hand cleansing and indicates that more attention should be given this process by employers or other executives in charge of personnel. To displace volatile solvents as hand cleansers, less harmful petroleum products of higher boiling range (as discussed by Klauder and Brill [3]) should be made available. If prolonged exposure of a worker's

10. White, R. P.: The Dermatergoses, or Occupational Affections of the Skin, ed. 4, London, H. K. Lewis & Co., Ltd., 1934, p. 339.

hands to a detergent solution is required, consideration should be given, as will be discussed, to the use of a nonalkaline one. A buffer ointment or solution should be used by workers whose work requires prolonged exposure of the skin to alkaline substances, a point which will be discussed herein. An emollient should be used by all workers engaged in wet work.

The necessity for some of these measures was stressed by Klauder, Gross and Brown.[11] These authors made a survey of some factories and workshops as to methods of hand cleansing. In contrast to the results of that survey (in 1939) are the more favorable results of a similar and more recent one reported by Lane.[12] Apparently more attention is now being given to hand cleansing, at least by large industrial plants.

PETROLEUM PRODUCTS AND OTHER CAUSES OF FOLLICULITIS

In previous studies petroleum products other than the more volatile fractions (classified under primary irritants) were sufficiently encountered as causes of occupational dermatoses to merit separate classification.

In these studies the most frequent cause of occupational folliculitis was mineral oil. In a consistent manner the most frequent cutaneous reaction to mineral oil was oil folliculitis (oil acne, oil boils).

In the 614 additional cases of occupational dermatoses now reported occupational folliculitis was less frequently encountered—in 38 of the 614 cases compared with in 116 of 1,059 cases of occupational dermatoses reported previously.[1] This observation is doubtless explained by the curtailed use of mineral oil comprising cutting oil incident to cessation of warfare.

Of the 38 cases of folliculitis the majority were caused by mineral oil and by certain chlorinated hydrocarbons (chloracne), with the remaining ones caused by a variety of dust—bone dust, bakelite® (without sensitization dermatitis), clay, cement, flour and sugar.

Description of the eruption of oil folliculitis, chloracne and folliculitis from dust (dust eruption) is afforded in previous reports and need not be reiterated.

PHYSICAL AND BIOLOGIC AGENTS

In accordance with the method of classification employed in this study, physical and biologic agents were the least among the causes of occupational dermatoses. Of the additional 614 cases of occupational dermatoses now reported there were 18 of divers dermatoses from these sources.

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11. Klauder, J. V.; Gross, E. R., and Brown, H.: Prevention of Industrial Dermatitis, Arch. Dermat. & Syph. **41**:331-356 (Feb.) 1940.

12. Lane, C. G.: Cutaneous Cleansing for Industrial Workers, J. Indust. Hyg. & Toxicol. **31**:220-226 (July) 1949.

Cutaneous reaction to spun glass was the most frequent (7 of the 18 cases). Lupus erythematosus was observed on the face of two welders. An alleged defect in the mask of one and carelessness in its use by the other worker were reasonable explanations of undue exposure to ultraviolet rays as a precipitating agent in causing the eruption.[13]

Erosio interdigitalis blastomycetica occurred in a worker engaged in canning fruit.

The bites of different parasites were observed among different workers. Included were the cases of a group of girls who presented lesions suggesting the bite of a parasite. A reasonable source was dead rats found in their work room.

EFFECT OF ALKALI ON THE SKIN

In Burckhardt's studies [14] of the sensitivity of the skin to alkali, its capability to neutralize alkali and the dermatitis due to alkali, notably that of masons, he concluded that decreased resistance of the skin to alkali (toxic hypersensitivity), rather than an allergic hypersensitivity, is an important etiological factor in this form of dermatitis. Toxic hypersensitivity concerned impaired function of the skin to neutralize alkali.[15]

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13. Although the role of nonoccupational exposure to ultraviolet rays could not be evaluated, the insurance carrier recognized an occupational phase in causation.

14. (*a*) Burckhardt, W.: Beiträge zur Ekzemfrage: Die Rolle des Alkali in der Pathogenese des Ekzems speziell des Gewerbeekzems, Arch. f. Dermat. u. Syph. **173**:155-167, 1935; (*b*) Das Maurerekzem (Eine experimentelle und klinische Studie zur Ekzemfrage), ibid. **178**:1-44, 1938; (*c*) Neuere Untersuchungen über die Alkaliempfindlichkeit der Haut, Dermatologica **94**:73-96, 1947.

15. Space permits only brief description of the technic Burckhardt now employs.[14c] In the neutralization test one drop of 1/80 N sodium hydroxide is placed on the skin and then one drop of an alcoholic solution 1:2,000 of phenolphthalein. This mixture is covered with a glass block, and the time of disappearance of the red discoloration is noted. This procedure is repeated at the same site for 10 consecutive times. The results are graded as follows: in quick neutralization the red discoloration disappears in not more than five minutes; in the mean or average the disappearance requires five to seven minutes, and in slow it exceeds seven minutes. Burckhardt observed that patients with dermatitis attributed to alkaline substances showed results predominantly indicative of slow neutralization.

In the sensitivity test one drop of 0.5 N sodium hydroxide is placed on the skin and covered with a glass block and allowed to remain for 10 minutes. This procedure is repeated until the following symptoms appear—sense of burning and redness accompanied with minute vesicles. The alkali-sensitive skin reacts after the first or second test. In the absence of reaction no more than eight tests are performed.

Burckhardt prefers the sensitivity test if only one of the two aforementioned tests is performed.

In our experience the neutralization and sensitivity tests of Burckhardt are time consuming and not practical as an office procedure. Moreover, we purposely conducted sensitivity tests on patients with diffuse eczematous dermatitis unrelated to alkali exposure. Some reacted after application of the second drop of the sodium hydroxide solution, placing them in the category of alkali-sensitive persons. In addition an eczematous patch appeared at the site of the test. This observation suggests that alkali sensitivity is an attribute of the eczematic skin and may not be the expression of a selective dysfunction of the skin. The question therefore arises whether these tests have differential value.

The Effect of Soap on p_H of Skin.—Preliminary to determining the effect on the p_H of the hands after variable exposure to soap we studied the p_H of the hands of normal persons and of patients with dermatitis of the hands, including those whose dermatitis was attributed to alkali.[16]

The p_H of the hands ranged from 4.5 to 6.5.[17] Frequently that of the palm was from 0.2 to 0.5 unit higher than that of the dorsum. The p_H was not maintained constantly at the same level; readings every 15 minutes for several hours showed slight variations ranging from 0.1 to about 0.4 unit. A p_H above 6.5 could invariably be ascribed to hand washing with soap within the preceding hour or, in the case of women, to dishwashing within the preceding several hours. A p_H below 4.5 was observed in summer, especially on hot humid days when the skin at the site of the test would be moist with perspiration. Under these circumstances a p_H as low as 3.5 was observed.[18]

There was no variation from the aforegoing observations in determinations made on patients with variable degrees of dermatitis of the hands (except that serum on the surface of eczematous patches was on the alkaline side), including patients with dermatitis of the hands from exposure to alkali and also persons without dermatitis whose work entailed prolonged exposure to alkaline substances.

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16. In the entire studies herein reported p_H determinations were made with the glass electrode of either a Beckman potentiometer or a Coleman potentiometer.

17. The norm for the hydrogen ion concentration of skin surface and sweat (compiled from the literature by Beerman) as determined by the universal indicator and capillaries and also by vacuum tube potentiometer with glass electrode is given in Sunderman, T. W., and Boerner, T.: Normal Values In Clinical Medicine, Philadelphia, W. B. Saunders Company, 1949, p. 479.

18. Others report on a rise of p_H after washing with soap, a lower p_H of the sweat-bathed skin and therefore better tolerance for soap in summer. Discussion with bibliography is afforded by Bernstein, E. T., and Herrmann, F.: The Acidity on the Surface of the Skin, New York State J. Med., **42**:436-442, 1942, and Guillot, C. F.: El p_H cutaneo, Buenos Aires, Liberia y editorial "El Ateneo," 1949. We know of no reported study of observations on patients after prolonged exposure to soap and in other phases as herein reported.

After a hand washing with toilet cake soap[19] with warm running water lasting ½, one and two minutes the p_H immediately after drying the hands increases, the increase ranging from about 0.6 to 1.8 unit. This increase occurs on both the dorsum and the palm, that on the latter usually being more than that on the dorsum and doubtless explained by more contact with the soap. After a hand washing lasting two minutes the increase, up to about 7 or above, especially on the palm (fig. 4), gradually declines to the p_H at the onset of the hand washing in a period ranging from about 45 minutes to more likely one to 1½ hours and for some persons as long as two to 2½ hours. If the duration of the hand wash is three minutes or longer, as in a 10 minute wash as practiced by surgeons, or if exposure to soap is still longer, as in dish-washing, the rise of p_H is uniformly above 7.

It was observed that the p_H, which rose to above 7 immediately after a 10 minute surgical "scrub-up," had decreased to about normal when

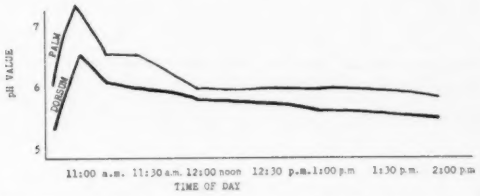

Fig. 4.—The curve of the p_H after a two minute hand washing with cake soap in warm running water. The peak of the rise was immediately after the hand washing.

again determined after removal of the rubber gloves ½ hour to one hour after the "scrub-up".[20]

In the case of women washing dishes for periods ranging from 15 minutes to one hour, the p_H rose to between 7 and about 8.5. After cessation of washing the p_H gradually declined to the level prior to dish-washing in from 2 to 4 and 4½ hours.

Further rise of p_H and duration of such rise beyond that stated in the aforegoing comments was in relation to duration of continuous or frequency of intermittent exposure to soap solution.

Figure 5 shows the curve of p_H of the palm and dorsum after a washing with cake soap for 15 seconds every 15 minutes for 3 and ¾ hours.

19. The p_H of a 1 per cent aqueous solution (with distilled water) of 36 toilet soaps ranged from 9 to 11.[11]

20. It is reasonable that the buffer action of sweat under the rubber gloves and the p_H of 5.9 of the talc (one sample tested) applied on the hands and inside the gloves facilitated a quicker return of p_H to normal. This action of sweat may act to prevent dermatitis from excessive hand washing and possibly, too, infection of the hands.

It is seen that p_H of the palm in contrast to the dorsum rose and remained above 7 as long as hand washing was continued.

The upper curve of figure 6 represents the p_H of the left dorsum before hand washing (B) and immediately after hand washing (A). Both hands were washed with cake soap seven times at irregular intervals for 3¾ hours. In contrast to figure 5, the p_H did not rise to 7 and the rise was less maintained. Apparently the irregular interval between hand washings afforded an opportunity for the skin to neutralize the alkalinity of the soap solution.

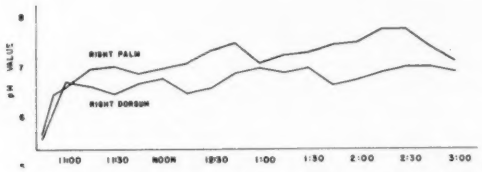

Fig. 5.—The curve of the p_H of the right dorsum and palm after washing with cake soap for 15 seconds with running water (60-64 F.) every 15 minutes. The curve starts just prior to the initial hand washing at 10:45 a. m. The last hand washing was at 2:30 p. m.

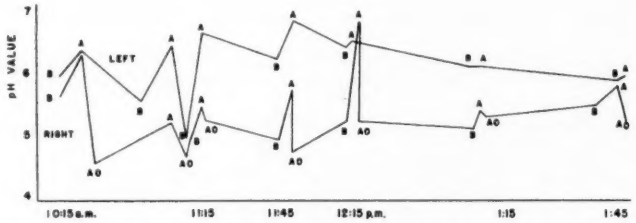

Fig. 6.—Both hands were washed seven times in 3¼ hours with cake soap for 15 seconds, and buffer ointment (acetic acid, p_H 2.8) was applied to the right dorsum immediately after washing. The upper curve represents the p_H of the left dorsum, and the lower curve, that of the right dorsum. B represents the p_H determination before washing, and A, the determination immediately after washing. Three p_H determinations were made—before the washing (B), after the washing (A) and after application of the buffer ointment (AO).

The lower curve of figure 6 represents the p_H of the right dorsum before hand washing (B), immediately after hand washing but before application of a buffer ointment (A) and after such application (AO). The p_H of the buffer ointment was 2.8; it was comprised of acetic acid, 2 Gm.; wool fat, 40.6 Gm., and petrolatum, 60.0 Gm. After each hand wash this ointment was spread over the dorsum; the latter was wiped with a cloth, and p_H determination was then made. The residue of the

ointment remained until the next hand washing. It is seen that thus the p_H of the right dorsum was maintained below 5.6, which was the reading at the onset of the study.

The influence of intermittent exposure to soap solution through the work day is shown in figures 7 and 8. The two (Negro) workers repre-

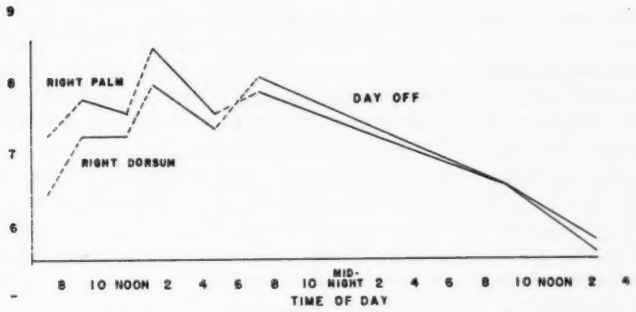

Fig. 7.—The curve of the p_H of the hands of a 50 year old Negro pot and pan washer, intermittently exposed throughout the work day. (The subject had worked at this occupation for four years.) The normal range was not attained until the worker's day off, 19 hours after cessation of work. The broken line indicates duration of washing, and the solid line, cessation of washing. The p_H of the soft soap solution was 9.2.

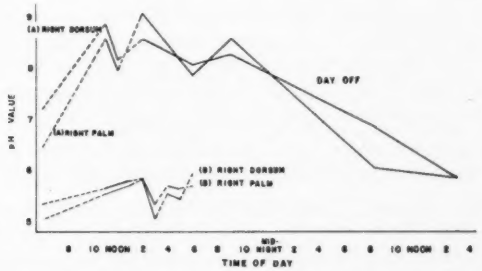

Fig. 8.—The upper curve indicates the p_H of the hand of a pot and pan washer after intermittent exposure to soap powder solution (A, p_H 10.8) throughout the work day. (The subject had worked at this occupation for one year.) A normal p_H was reached 20 hours after cessation of work. The lower curve is for the p_H of the same worker's hand when a nonsoap detergent (B, p_H 5.1-6.5) was employed for the same wash job. The broken line indicates duration of washing, and the solid one cessation of washing.

sented in these figures were pot and pan washers [21] in the kitchens of two different institutions. The hands and most of the forearms were

21. Unlike the situation with dishes, there is no mechanical appliance employed in the washing of large pots and pans.

immersed in a soap solution throughout work. The p_H determinations for the solutions were 9.2 and 10.8. The workers started work between 6 and 7 a. m., and the last wash job was between 6 and 7 p. m. It is seen in figures 7 and 8 that the p_H determinations for the palms and dorsa were above normal on the subjects starting work and rose thereafter and remained well above 7 throughout the work day. The variation in the curves was in relation to washing and temporary cessation of work. It is observed that the p_H of their hands was still above normal up to the time they went to bed (about 10 p. m.) and also when they resumed work the following morning. It was therefore necessary to study the p_H of their hands during their day off in order to determine the time required after cessation of work for the p_H to become within the normal range. As shown in the figures, this period was 19 hours for one (fig. 7) and 20 hours for the other (fig. 8). The hands were not washed with soap after the stopping of work but were rinsed and dried, and a request was made for the subjects to refrain from hand washing or other exposure to alkaline substances (other than the wash job) during the study period.[22]

The lower curve in figure 8 represents the p_H curve of the hand of the same worker (represented in the upper curve) during the use of a nonsoap detergent instead of soap powder for the same washing job. As was expected, the p_H of the hand did not rise above the p_H of the solution of the nonsoap detergent.

Figure 9 represents the curve of p_H of the hands of another worker, a dishwasher (white male). It is seen that the p_H at the onset of work was much lower for him than for the two pot and pan washers (figs. 7 and 8) and that the rise of the p_H during work was less and the descent to normal or almost normal much quicker [23] than for them.

Change in p_H of Infants' Skin After Washing.—Study was made of the p_H of the skin of 20 infants, male and female, ranging in age from 2 to 15 days. The p_H of the abdomen, one forearm and one thigh was determined eight hours after the infant was bathed in soap and water. These determinations were regarded as normal and were compared with determinations made on the same regions about three hours after the bath. The p_H of the soap solution was 9.8.

22. After cessation of work the hands and forearms of these two workers were dry and covered with a fine scale. One regularly used petrolatum as an emollient, and the other used a hand lotion, the p_H of which (ironically) was 8.5. Use of the hand lotion was discontinued during the study period. Since the workers were Negroes (the skin was quite dark), neutralization tests and tests of sensitivity to alkali did not give satisfactory results.

23. It is reasonable that the shorter duration of employment as a dishwasher—four months—is one phase in explanation of the difference between the curve of the p_H of this worker and those of the two pot and pan washers.

Eight hours after the bath the range of p_H of the regions tested was 4.6 to 5.72, the average being 5.59. Three hours after the bath the range was 5.2 to 7.2 and the average was 6.16. The p_H of one or the other of the three regions tested in four of the 20 infants three hours after the bath was 7 or slightly above.[24] These results are comparable to the rise of p_H after hand washing for five minutes or longer.

Change of p_H in Relation to Degree of Alkalinity.—It is reasonable that after exposure of the skin to any alkaline substance, detergent or otherwise, the change in the p_H of the skin will correlate the curves shown in figures 4 to 9 in relation to frequency and duration of such exposure and degree of alkalinity compared with that of soap.

According to Lane and Blank [25] pure soap solutions have a range of alkalinity equivalent to $\frac{1}{7,000}$ to $\frac{1}{300}$ N sodium hydroxide solution, approximately 0.006 to 0.013 Gm. of sodium hydroxide per 100 cc. of water. The latter dilution was employed by several different persons in alternately immersing and rinsing their hands for one minute and for

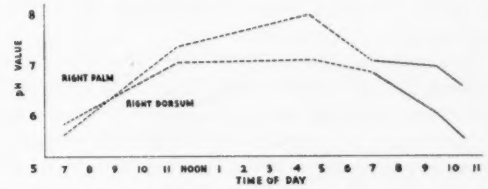

Fig. 9.—The curve of the p_H of the hands of a 51 year old white male dishwasher, exposed intermittently to soap solution throughout the work day. (The subject had been a dishwasher for four months.) In contrast to the situation for the workers represented in figures 7 and 8, the rise of the p_H of the hands of this worker during work was less and normal range after cessation of work was attained sooner. The line composed of short dashes indicates the duration of washing; that made up of long dashes, wet work and washing at intervals, and the solid line, cessation of washing. The p_H of the soft soap solution was 9.5.

two minutes. The change in the p_H of the hands after this procedure showed no great difference from that occurring after washing with soap for a comparable period.

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24. It is interesting to note that the "no bath technic" has been advocated in prevention of impetigo neonatorum. Some writers (Fischer, C. C.: Prevention of Impetigo Neonatorum: Clinical Study of Various Methods Including Use of New Antiseptic Baby Lotion, Arch. Pediat. **61**:352, 1944) have shown reduction in its incidence following cessation of washing infants with soap and water. Whether this can be attributed to maintenance of the normal p_H of the skin we are unable to state. In this regard it is to be noted that the defensive mechanism of the skin is less developed in infants and that the buffer action of sweat would be less operative in them than in adults.

25. Lane, C. G., and Blank, I. H.: Cutaneous Detergents, J. A. M. A. **118**: 804-817 (March 7) 1942.

As later discussed, exposure of the hands for ½ minute to a 0.14 per cent solution of sodium hydroxide caused a rise of the p_H after which the p_H did not become normal until an elapse of four hours and 20 minutes.

These observations suggest that the rise of p_H and period required for its restoration to normal correlate the degree of alkalinity to which the skin is exposed.

No study similar to the aforegoing was made in the case of patients with an eczematic skin.

It should be emphasized that in evaluation of the change in the p_H of the skin after exposure to soap (indeed, to other alkaline substances) as herein reported, the role of the buffer action of sweat should be considered. Evaluation of this role becomes difficult in consideration of its variation in different persons and the influence of emotional reaction, physical exercise, clothing, external temperature, seasons of the year and geographic location.

Irritant Action of Soap.—It is not our purpose to discuss all phases in explanation of the irritant action of soap on the skin. The two following phases are, however, pertinent.

Blank's studies [26] incriminated the fatty acids, especially certain types and amounts of the various fatty acids. He concluded that the saturated fatty acids of lower molecular weight (caproic, caprylic and capric acids, present in the mixed fatty acids of coconut oil, predominantly used in the manufacture of soap) are primary cutaneous irritants. As the molecular weight increases above that of caprice acid irritant action becomes less, but such action is exerted as the p_H of the skin rises above normal. This action was less apparent with stearic and with palmitic acids; these fatty acids, however, are not extensively used in the manufacture of soap.

In accordance with the study of Blank, all soap would act as an irritant at a sustained rise in the p_H of the skin, as shown in figures 5, 7, 8 and 9.

According to the thesis of Burckhardt prolonged exposure to alkali impairs the function of the skin to neutralize alkali and predisposes to dermatitis.

THE p_H OF PRESENT DAY DETERGENTS

Stokes,[27] in discussing soothing applications in dermatotherapy, writes of ". . . . the preservation of the 'acid mantle' by avoiding the raising of the p_H by any agent, especially soaps. The modern detergents are effective non-alkalinizing cleansers."

26. Blank, I. H.: Action of Soap on Skin: I. Patch Test with Fatty Acids, Arch. Dermat. & Syph. **39**:811-824 (May) 1939.

27. Stokes, J.: "Simplifying" Dermatology for the Practitioner, Pennsylvania M. J. **52**:1065-1071 (July) 1949.

The question arises, which ones? Only for the detergents advertised to dermatologists for use by patients who are intolerant to soap or who have dermatitis of the hands is information given regarding the p_H (table 1). For other "modern" detergents (table 2), a group comprised of an increasing number of sulfated esters, ethers and alcohols, so-called wetting agents sold for kitchen and household use and still

TABLE 1.—*P_H of Nonsoap Detergents for Patients Intolerant to Soap or with Dermatitis*

Name of Detergent	p_H	Dilution
Acidolate*	6.1	Undiluted
Lowila*	6.75	1 per cent
Dermolate*	8.4	1 per cent
pHisoderm*	5.5	Undiluted
Vel* beauty bar	6.6	1 per cent
Tersus*	6.8	Undiluted
Lamkin* soap cream	7.8†	Undiluted

* Registered trademark.
† Only one sample tested; p_H given by manufacturer as approximately 7.62.

TABLE 2.—*P_H of Nonsoap Detergents for Kitchen and Household Purposes*

Name of Detergent	p_H, 5% Solution	Name of Detergent	p_H, 5% Solution
Vel* (Colgate-Palmolive-Peet Company)	6.2	Joy* (Procter and Gamble)	7.2
Tide* (Procter and Gamble)	9.9	Spin* (Climalene Company)	10.2
Dreft* (Procter and Gamble)	7.2	Dif* (Dif Corporation)	12.1
Breeze* (Lever Brothers)	7.8	Surf* (Lever Brothers)	8.0
Ultrawet* 60L (Atlantic Refining Co.)	7.0	Fab* (Colgate-Palmolive-Peet Company)	11.1
Ultrawet* SK (Atlantic Refining Co.)	7.6	Hum* (Theobald Indust.)	10.2
Glim* (B. T. Babbitt, Inc.)	7.8	Spic and Span* (Procter and Gamble)	10.2
Sweri* (H. J. Heinz Co.)	7.2	Terjolate* (Rare Chemicals Inc.)	9.6
Shina Dish* (Perfex Company)	7.9	Lowila* (liquid) (Foster-Milburn Co.)	7.9
Disho* (The M. Werk Co.)	6.7		

* Registered trademark.

others for industrial uses, no such information is given. Apparently the manufacturers are (unfortunately) not concerned with the p_H of their preparations in relation to whether or not they alkalinize the skin. The following studies were therefore necessary to answer the foregoing question.

Nonsoap Detergents.—Table 1 gives the p_H of nonsoap detergents commercially available for patients whose skin is intolerant to soap or who have dermatitic hands.

Table 2 gives the p_H of nonsoap detergents for kitchen and household purposes.

Hand Cleansers for Industrial Workers.—We studied 103 different detergents made by 62 different manufacturers and sold as hand cleansers for industrial workers. Of the 103 detergents four were abrasive pastes (grit paste hand soap), with a p_H (undiluted) ranging from 8.9 to 11; two were abrasive (grit) cake soap, the p_H (1 per cent solution) being 9.3 and 10.5, respectively; 16 were liquid soaps,[28] the p_H (50 per cent dilution with water) ranging from 9.2 to 11.7; 10 were nonsoap detergents in liquid form,[28] the p_H (undiluted) ranging from 7.4 to 10 for six and 5.5 to 6.7 for four; 57 were gritty powders (hand scouring powder), the p_H (2 per cent solution) ranging from 9.2 to 10.7 for 55, with that of the remaining two being 7 and 6.9, respectively, and 14 were waterless hand cleansers, so-called dry cleansers, the p_H (undiluted) ranging from 7.15 to 8.15 for 11 and being 6.6 for two and 6.9 for one.

It was definitely established that four of the 57 gritty powders contained a synthetic detergent, although the presence of one was suspected in a greater number. Of the four containing a synthetic detergent all but one were alkaline. This one exception was the only one of 52 samples tested that did not react to the tests for an alkaline salt detergent (an alkaline carbonate, one of the phosphates or a borate). An alkaline carbonate was evidenced by effervescence when concentration hydrochloric acid was added to the powder or to a solution of it. The reaction to this test was positive for 27 of the 52 samples. The presence of a phosphate or borate was evidenced by a heavy white precipitate after calcium chloride was added to a solution of the powder. This precipitate was dissolved after acidification with acetic acid (excluding an oxalate). This test gave a positive reaction with all but one of 52 samples. The presence of borate was determined by testing with tumeric paper. This test gave a positive reaction with 15 of the 52 samples. For some samples which reacted positively the label stated the presence of sodium borate (borax). Apparently then a phosphate (presumably trisodium) was the most frequent alkaline salt additive.

The waterless or dry cleaners are employed without the use of water. They are newcomers in the field of cutaneous detergents. The samples studied were either transparent jelly-like mixtures, clear syrup-like liquids or (the majority) creams that liquefied on exposure to air. They were sold to be used to remove paint, varnish, lacquer, hectograph,* mimeograph* and other inks, grease, grime and other foreign matter. As determined from our questioning of industrial workers as to methods of hand cleansing, their use is increasing.

28. A few of the liquid soaps and the liquid nonsoap detergents contained an antiseptic and were advised for cleansing of wounds and prevention of infection of the hands of industrial workers. In the case of some the label stated that the antiseptic was hexachlorophene (*bis*[2-hydroxy-3,5,6-trichlorophenyl]methane; G-11).

According to Dr. Paul C. Campbell of the Division of Industrial Hygiene, United States Public Health Service,[29] in general they consist of a soap base such as triethanolamine, odorless kerosene or a lower boiling range petroleum solvent such as Stoddard solvent. Some contain ammonium hydroxide and a fatty substance such as hydrous wool fat. It was determined that the boiling range of the liquid that separated from several of the specimens we studied corresponded to that of kerosene.[3]

Comment.—Of the 103 hand cleansers for industrial workers 94 were alkaline, one was neutral and 8 had a p_H below 7.

In contrast to the observations in a similar study in 1939,[11] abrasive pastes and abrasive cake soaps are now losing in popularity and the use of gritty powders and soapless detergents is increasing. We see no great difference between many of the gritty powders employed by industrial workers as hand cleansers and soap powder and washing powder [30] employed for kitchen and household purposes. Comparison of our two studies show that soap as a hand cleanser has to some measure been displaced by the alkaline salt detergents, synthetic detergents [31] and petroleum solvents.

We regard as unfortunate the use of solvents as employed in the waterless cleansers. We see little difference between the use of some of these cleansers and the use of kerosene and gasoline as hand cleansers, discussed previously.

Other alkaline substances to which the worker is exposed are the following: some protective (barrier) cream and hand lotions; soluble cutting oils, or "soup," in the parlance of the worker, containing alkyl sulfonate or sodium sulfonate detergents and mineral oil (the p_H of the one we prepared in a 2 per cent solution in water [a commonly employed dilution] was 8.8), and ammonia water (diluted ammonia solution) and sodium hypochlorite (the last-mentioned substance, in a 5 per cent solution, comprises a number of bleaches used for kitchen, household and janitorial cleansing [a well known one is clorox®]. The p_H of one commercial preparation was 12. Eau de Javelle [a solution of potassium or sodium hypochlorite] is a similar preparation used for the same purpose).

29. Personal communication to the authors.

30. Soap powder should be distinguished from "powdered soap," which includes soap chips, soap flakes, granular soaps and soap beads also employed for household uses.

31. This observation is consistent with statistics that synthetic detergents now account for 25 per cent of all soap consumption in the United States (The Wall Street Journal, Dec. 24, 1949). Twenty per cent of Colgate-Palmolive-Peet Co.'s sale of detergents is comprised of sale of synthetic detergents (1949 Annual Report of Colgate-Palmolive-Peet Co.).

Sodium hypochlorite is also used as a hand cleanser, as is chemic. The latter is a mixture of sodium carbonate and calcium hypochlorite. A usual formula is 1 pound (0.45 Kg.) of each of these chemicals to 3 gallons (11.36 liters) of water. The alkalinity of this solution is the equivalent of that of a 0.14 per cent solution of sodium hydroxide, and so this dilution of sodium hydroxide (the p_H was 12.5) was employed to simulate the use of chemic as a hand cleanser. The hands were alternately immersed in the solution and rubbed over each other for ½ minute and then rinsed and dried. Immediately after the hands were dried their p_H was 8.5. The p_H remained above 7 for one hour and 40 minutes and reached the original level after an elapse of four hours and 20 minutes.

The same person on another day repeated the aforementioned procedure. After rinsing, the hands were immersed in a buffer solution (30 per cent solution of sodium bisulphite [$NaHSO_3$]), the p_H of which was 4.8, for 15 seconds and without rinsing in water were dried. Before immersion of the hands in the sodium hydroxide solution the p_H of the palm was 5.8 and that of the dorsum was 5.6. After immersion of the hands in the buffer solution and for the ensuing four hours the p_H remained below 6.

This observation stresses the desirability of employing a buffer solution after prolonged or intermittent exposure to alkaline substances.

SUMMARY

Report is made of an additional series of 1,412 cases of cutaneous diseases in patients who presented claims for compensation under the Pennsylvania law.

The cases previously reported and those now reported total 3,709; 2,850 of the patients were male and 859 female. The diseases of 1,673 (percentage of incidence, 45.08) were diagnosed as occupational in origin and those of 2,036 as nonoccupational.

The actual causes of the occupational dermatoses of the 1,673 are classified in the following groups, with the percentage of incidence: primary irritants (acids, alkalis and solvents [nonaqueous]), 28.6 per cent; trauma and accidental injury, 22.6 per cent; sensitizing substances, 13.6 per cent; wet work (water alone, soap and water and alkaline salt detergents), 13.1 per cent; cleansing agents applied to the skin, 10.7 per cent; petroleum products and other causes (hydrochlorinated hydrocarbons, vegetable oil and dust) of folliculitis, 9.2 per cent; and physical and biologic agents, 2.2 per cent.

Nonaqueous solvents were the predominating causal irritants. The trauma and accidental injury group included all dermatoses (18 different diseases of the skin) that resulted directly or indirectly from accident or injury. Substances causing sensitization dermatitis are enu-

merated. Wet work and methods of hand cleansing as causes of occupational dermatoses are discussed. Substances causing occupational folliculitis are enumerated.

Burckhardt's test of the ability of the skin to neutralize alkali and his test of its sensitivity to alkali are discussed.

The p_H of the hands of normal persons ranged from 4.5 to 6.5, and that of the sweat-bathed skin was lower.

The increase in the p_H of the hands after exposure to alkali and duration of such increase are in relation to the duration of continuous exposure, frequency of intermittent exposure and degree of alkalinity to which the skin is exposed. The most pronounced change of p_H and duration of change were observed in two pot and pan washers. It required about 20 hours after cessation of exposure to soap solution for the p_H of their hands to attain the normal range. The role of the buffer action of sweat is discussed. The effect of buffer agents on the p_H of the hands after exposure to alkaline solutions was studied.

Study was made of the p_H of the following commercial detergents: seven nonsoap detergents advised for dermatitic hands, 103 hand cleansers for industrial workers and 19 nonsoap detergents for kitchen and household purposes. Of the hand cleansers for industrial workers 94 were alkaline and 57 were gritty powders which predominantly contained one or more of the alkaline salt detergents.

1934 Spruce Street.

METABOLIC AND STEROID HORMONE CHANGES IN LUPUS ERYTHEMATOSUS

EUGENE F. TRAUB, M.D.
AND
HERBERT J. SPOOR, Ph.D., M.D.
NEW YORK

LUPUS erythematosus has been tentatively classified as one of the so-called collagen, or mesenchymal, diseases, not only as a result of the pathological work which has demonstrated fibrinoid degeneration [1] possibly due to precipitation of mucopolysaccharides from collagen ground substance [2] but also on the basis of the clinical response of the acute forms of the disease to adrenal cortical substitution or stimulation.[3] Recent extensive histological studies of the skin lesions by the Mayo group [4] stress vascular involvement in all stages of the disease and support the report that there is demonstrable interference with fluid exchange between vessels and tissue spaces.[5] The characteristic lesions of the skin are apparently not the primary manifestation of lupus erythematosus in that they do not account for the systemic pathology. Beyond the demonstration of the L. E. cell in acute forms of the disease [6] there are several other suggestive systemic observations. The major one of these is the high level of serum globulin, characterized by an elevated amount of the gamma fraction, which possibly leads to the high incidence of false positive syphilitic serologic reactions.[7] In addition, there is

From the Department of Dermatology and Syphilology, New York Medical College, Dr. Eugene F. Traub, chairman.

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1. (*a*) Klemperer, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, Arch. Path. **32**:569 (Oct.) 1941. (*b*) Klemperer, P.: The Pathogenesis of Lupus Erythematosus and Allied Conditions, Ann. Int. Med. **28**:1, 1948.

2. Klemperer.[1b] Altshuler, C. H., and Angevine, D. M.: Histochemical Studies on the Pathogenesis of Fibrinoid, Am. J. Path. **25**:1061, 1949.

3. Thorn, G. H.; Bayles, T. B.; Massell, B. F.; Forsham, P. H.; Hill, R. S.; Smith, S., III, and Warren, J. E.: Medical Progress: Studies on the Relation of Pituitary-Adrenal Function to Rheumatic Disease, New England J. Med. **241**:529, 1949.

4. McCreight, W. G., and Montgomery, H.: Cutaneous Changes in Lupus Erythematosus: Histopathologic Aspects, with Special Reference to Vascular Changes, Arch. Dermat. & Syph. **61**:1 (Jan.) 1950.

5. Kanof, N. B.: Physiologic Alterations in Lupus Erythematosus, New York State J. Med. **50**: 2443 (Oct. 15) 1950.

6. Haserick, J. R., and Sundberg, R. D.: The Bone Marrow as a Diagnostic Aid in Acute Disseminated Lupus Erythematosus, J. Invest. Dermat. **11**:209, 1948.

7. White, C. J.: The Problems of Positive Serological Tests for Syphilis in Lupus Erythematosus, Am. J. Syph., Gonor. & Ven. Dis. **31**:235, 1947.

a suggestive steroid hormone relationship demonstrated by the strong sex link of the disease, reported amelioration of the symptoms during pregnancy [1b] and response to adrenal cortical therapy.[8]

The role of the adrenal cortex in any of the collagen diseases has not been settled, and the specific disease picture of lupus erythematosus certainly does not fit into a picture based on the known functions of the purified adrenal steroids. These known functions—stimulation of gluconeogenesis and inhibition of carbohydrate utilization, regulation of sodium and potassium excretion and androgenic secretion leading to nitrogen retention—are all modified under therapy but only to a slight and often inconsistent degree.[9] Adrenal estrogenic and progestational components have been proved and must be considered, as also must be the physiological activities of the intact adrenal glands which have not been duplicated by the isolated sterols. The adrenal gland influences fat utilization and transport [10]; it also has regulatory effects on the immune status of the body, and somehow it is capable of building resistance to fatigue, vascular, muscular and mental.[11] If lupus erythematosus is related to adrenal cortical malfunction, the metabolic error may lie in one of the lesser known mechanisms. By study of various blood components in patients before, during and after steroid hormone therapy, one might approximate knowledge not only of the mode of action of the steroid but also of the systemic pathology of the disease itself.

We have studied cases of lupus erythematosus of the several types before, during and after steroid hormone therapy. Our objective has been twofold: first, to reveal, if possible, those metabolic values which are altered in the disease process and perhaps restored by substitution therapy, and, second, to make a metabolic comparison between disseminated and discoid lupus erythematosus. In this paper we are reporting blood studies on three representative cases of lupus erythematosus. These cases were diagnosed clinically and histopathologically as subacute disseminated (Qu), superficial discoid undergoing possible transition during pregnancy (Je) and chronic discoid (Su). Each of the patients had some disturbance in her menstrual picture. Qu, at 39, had experienced irregular menses since the onset of her lupus erythematosus symptoms, eight months earlier. Je, at 26, was five months pregnant and was experiencing an exacerbation of her lesions, which had first appeared after her first pregnancy, three years earlier. Su, at 47, had entered the menopause and had been having troublesome symptoms of that condition for about one year. She related onset of her discoid lesions to a hysterectomy 15 years earlier. None of the cases was sufficiently acute to permit demonstration of the Hargraves L. E. cell.

Metabolic studies were made initially shortly after admission while the patient was on the regular hospital diet. They were repeated after the patient had become

8. Baehr, G., and Soffer, L. J.: Treatment of Disseminated Lupus Erythematosus with Cortisone and Adrenocorticotropin, Bull. New York Acad. Med. **26**:229, 1950.

9. Elkinton, J. R.; Hunt, A. D.; Godfrey, L.; McCrory, W. W.; Rogerson, A. G., and Stokes, J., Jr.: Effects of Pituitary Adrenocorticotropic Hormone (ACTH) Therapy, J. A. M. A. **141**:1273 (Dec. 31) 1949.

10. Hartman, F. A., and Liu, T. Y.: Secretion of Fat Factor of the Adrenal, Federation Proc. **9**:57, 1950.

11. Hartman, F. A., and Brownell, K. A.: The Adrenal Gland, Philadelphia, Lea & Febiger, 1949.

established on a rigidly controlled balance study diet consisting of a total of 1,700 calories daily in a liquid diet containing milk, eggs, strained baby food and cereal. Hormone therapy with Δ^{5}-pregnenolone, 300 to 400 mg. per day for four days by intramuscular injection, was administered and the blood studies repeated. Then administration of the drug was stopped while the dietary conditions remained unchanged, and, after a four day period to permit restoration of what we hoped would be the control level, the blood studies were repeated. At this point, only one of the patients had responded favorably clinically. Qu, the patient with subacute disseminated lupus erythematosus, had practically complete clearing. Both forms of discoid lupus erythematosus showed no response to the short period of therapy.

The blood data obtained during these study periods were interesting. Each subject served as her own control, but we have included for comparison data obtained from a practically normal 16 year old girl who had been subjected to the

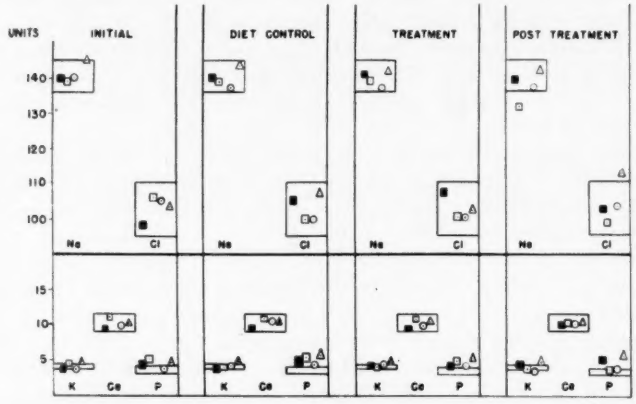

Fig. 1.—Comparison of blood electrolytes in three patients with lupus erythematosus and in one control patient. The black square indicates the control patient (Ga); the white square, the patient with disseminated lupus erythematosus (Qu); the circle, the patient with transitional discoid lupus erythematosus (Je), and the triangle, the patient with chronic discoid lupus erythematosus (Su). Normal ranges of values for blood sodium, chloride, potassium, calcium and phosphorus are blocked in.

identical routine (Ga, with the diagnosis of erythema induratum of Bazin). Figure 1 compares the blood electrolytes. Sodium, chloride, potassium, calcium and phosphorus values are given. For comparison, our laboratory normal ranges for each substance are blocked in. Electrolyte changes were insignificant except for a slight elevation in the serum phosphorus. As the control girl showed the same elevation, this was probably attributable to the diet. The post-treatment fall in sodium in Qu, the patient with the disseminated form of the disease, was of interest, but there was nothing with regard to it to characterize either the disease or the therapy.

Figure 2 shows the serum protein levels. The identifying symbols indicate individual albumin-globulin ratios, while the broken lines mark the albumin and globulin levels maintained during each period by Ga, the control. Treatment def-

initely decreased the globulin fraction, particularly in subjects Qu and Je. The post-treatment elevation would be much more significant had patient Ga not responded in similar manner. The labile component was in the globulin fraction.

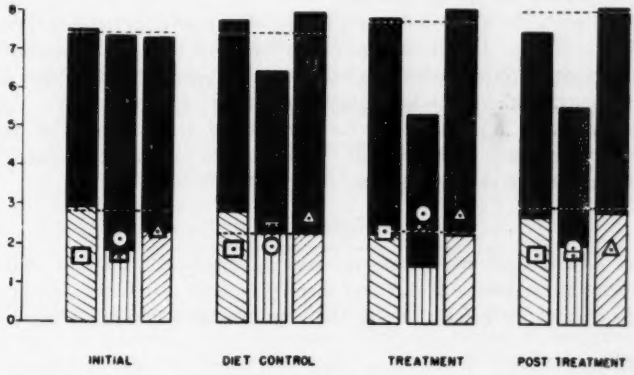

Fig. 2.—Serum protein levels for three patients with lupus erythematosus and for one control patient. The square indicates the patient with disseminated lupus erythematosus (Qu); the circle, the patient with transitional discoid lupus erythematosus (Je); the triangle, the patient with chronic discoid lupus erythematosus (Su), and the rectangle, the control patient (Ja). Broken lines mark the albumin and globulin levels maintained by the control patient during each period. Solid portions of the graphs indicate albumin levels, and hatched ones, globulin levels. The position of the symbol indicates the albumin-globulin ratio for each patient.

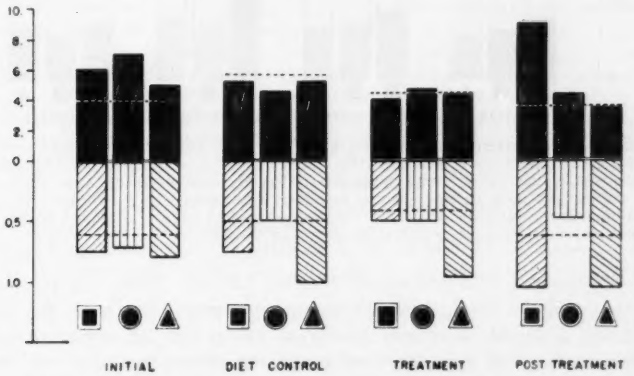

Fig. 3.—Serum uric acid and creatinine levels for three patients with lupus erythematosus and for one control patient. The square indicates the patient with disseminated lupus erythematosus (Qu); the circle, the patient with transitional discoid lupus erythematosus (Je), and the triangle, the patient with chronic discoid lupus erythematosus (Su). Broken lines indicate levels maintained during each period by the control patient (Ga). Solid portions of the graphs indicate uric acid, and hatched ones, creatinine.

Figure 3 depicts the serum uric acid and creatinine levels of the series in direct comparison with those of the control girl. There was shown a definite lability apparently associated with the disease. Diet alone tended to normalize the high level of uric acid; therapy lowered the levels, and cessation of therapy gave a

release with a return to elevation. The conditions of Qu again responded most definitely. Creatinine values were high throughout except for Je, the pregnant girl, whose low post-treatment value was inexplicable. High creatinine levels may possibly be part of the disease process.

Figure 4 gives the blood cholesterol levels. The total cholesterol is divided into free and ester forms. Levels for the control remained reasonably constant after a slight dietary elevation of levels of both forms of cholesterol. In the lupus erythematosus patients, both fractions behaved strangely under therapy. Qu, who responded favorably to pregnenolone therapy, showed definite lability of cholesterol levels in both free and ester fractions. The changes for the others were beyond normal limits but not clearly defined.

CONCLUSIONS

These data on patients with three types of lupus erythematosus subjected to nearly identical conditions of diet and therapy indicate some variation in stability of blood constitutents before, during and after steroid hormone therapy.

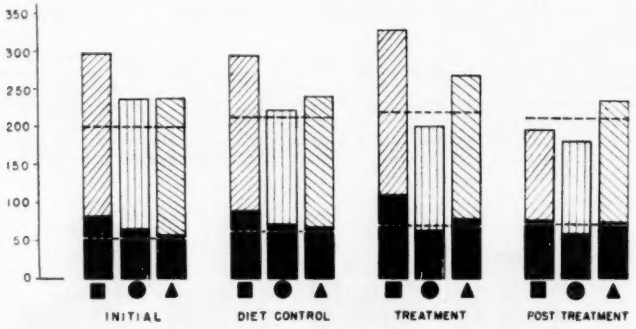

Fig. 4.—Blood cholesterol levels for three patients with lupus erythematosus and for one control patient. The square indicates the patient with disseminated lupus erythematosus (Qu); the circle, the patient with transitional discoid lupus erythematosus (Je), and the triangle, the patient with chronic discoid lupus erythematosus (Su). Broken lines indicate levels maintained during each period by the control patient (Ga). Hatched portions of the graphs indicate cholesterol ester, and solid ones, free cholesterol.

The electrolyte system was not significantly altered. There was an abnormally high serum globulin level, some disturbance in serum uric acid and creatinine behavior and a definite abnormal lability of values for the free cholesterol and cholesterol esters. The daily injections of 400 mg. of pregnenolone were continued in all cases for at least three months after the experimental period.

No sharp conclusions can be drawn from these cases, but it is important that in the subacute disseminated lupus erythematosus patient whose blood constituents were most affected, therapeutic response to pregnenolone was rapid, and apparently at least temporarily curative.

Dr. T. H. McGavack and his staff at the New York Medical College, Metropolitan Hospital Research Unit, cooperated with us in this study.

The pregnenolone used in this study was furnished by Dr. Edward Henderson of the Schering Corporation, Bloomfield, N. J.

EFFECTS OF CORTISONE ON ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS

LOUIS A. BRUNSTING, M.D.*
CHARLES H. SLOCUMB, M.D.‡
AND
JOHN W. DIDCOCT, M.D.
Fellow in Dermatology and Syphilology, Mayo Foundation
ROCHESTER, MINN.

AFTER THE demonstration by Hench and his associates [1] of the favorable influence of adrenal cortex hormone, 17-hydroxy-11-dehydrocorticosterone (cortisone), and pituitary adrenocorticotropic hormone (ACTH) on the course of rheumatoid arthritis, it was only a matter of time and availability of the hormones until study of the effects of these substances was extended to include other members of the so-called collagen group of diseases, particularly rheumatic fever,[2] periarteritis nodosa [3] and disseminated lupus erythematosus.[4]

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* From the Section on Dermatology and Syphilology, Mayo Clinic.
‡ From the Division of Medicine, Mayo Clinic.

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1. (*a*) Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: The Effect of a Hormone of the Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis: Preliminary Report, Proc. Staff Meet., Mayo Clin. **24**:181-197 (April 13) 1949. (*b*) Effects of Cortisone Acetate and Pituitary ACTH on Rheumatoid Arthritis, Rheumatic Fever and Certain Other Conditions: A Study in Clinical Physiology, Arch. Int. Med. **85**:545-666 (April) 1950. (*c*) Sprague, R. G.; Power, M. H.; Mason, H. L.; Albert, A.; Mathieson, D. R.; Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: Observations on the Physiologic Effects of Cortisone and ACTH in Man, ibid. **85**:199-258 (Feb.) 1950.

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The typical clinical features of disseminated lupus erythematosus [5]—the eruptive phenomena, arthritis, serous effusions and nephritis—as well as other far reaching systemic implications of the disease need not be elaborated here except to emphasize the high incidence of involvement in young women, the hyperreactive qualities of these patients, the insidious nature of the masked symptoms in the early phases and the tendency toward a course of recurrent relapses and remissions extending sometimes over a period of years. In many cases there is a record of infectious episodes and other insults before symptoms appear, as happens in rheumatic fever. The cause of lupus erythematosus is unknown. Urticaria, purpura, sensitivity to sunlight and the occurrence of anaphylactoid reactions, which also color the history of patients with periarteritis nodosa, are well known, but no specific incriminating agent has been identified. Leukopenia and thrombocytopenia are regular features of the acute phase of the disease, as are an increase in concentration of serum globulin and a remarkable change in the quality. The last change is indicated by the unique effect which appears in vitro on certain cells of the bone marrow and the peripheral blood.[6]

The pathological changes in disseminated lupus erythematosus are similar in many respects to those which occur in rheumatic fever, periarteritis nodosa and scleroderma in that the condition is a diffuse vascular disease. Lupus erythematosus affects particularly the kidneys, spleen and heart. Occasionally it produces nonbacterial vegetative endocarditis, and there is a peculiar hyaline or fibrinoid reaction of the connective tissue described as collagenous degeneration or, more aptly, a reaction of the mesenchymal tissues in general.[7] In lupus, these effects are minimal in the skin, in contrast to the situation in scleroderma.[8] The grouping of the various collagen diseases together because of the similarity of their general pathological pattern by no means implies that they are related etiologically.

In February 1949 we first administered cortisone to a patient who had acute disseminated lupus erythematosus. In this case we observed for the first time an agent capable of exerting some measure of control over the progressive decline

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usually associated with acute disseminated lupus erythematosus. Subsequently we have extended our observations by the administration of cortisone and ACTH to six additional women in the acute phase of the disease, there being a fatal termination in three instances. Our experiences concerning the therapeutic limitation of these hormones in the control of lupus erythematosus as well as the physiological alterations in the patients under observation form the basis for this report.

REPORT OF CASES [9]

CASE 1.—This patient, a housewife 32 years old, was admitted directly to the hospital under our care early in February 1949. She presented the characteristic signs of the acute phase of disseminated lupus erythematosus; only the cutaneous features of the disease were lacking. Early in 1947 appendectomy had been done because of subcostal and vague abdominal pains, but the appendix was reported to be normal. Symptoms of fatigue and weakness persisted throughout the summer months without apparent cause. In December 1947 the patient was married and soon became pregnant. During the first month of the pregnancy urticaria appeared off and on for several weeks. In March 1948, when the patient had been pregnant for about three months, arthralgia, synovitis, albuminuria and some edema developed. Exposure to the sun brought on chilly sensations but no rash. In midsummer of 1948 the patient was confined to the hospital for seven weeks with pneumonia and pericarditis. Penicillin and blood transfusions were employed, and there was one transfusion reaction with chills and fever. In September 1948, one week after the delivery of a normal child, the patient's malaise, weakness and arthralgia were aggravated by the development of fever, synovitis and albuminuria; leukopenia was noted for the first time. During the eight weeks of her stay in the hospital, these features became more pronounced, dyspnea and thoracic pain appeared and the swellings and pains in the joints became the chief source of discomfort. In spite of supportive measures, the patient's condition declined progressively in the next several months.

On admission the patient was acutely ill with fever, emaciation, polyarthritis and synovial effusions affecting particularly the joints of the hands and feet and the elbows and knees. The heart was enlarged, and pleural and pericardial friction rubs were present. There was diffuse abdominal tenderness, and the liver and spleen were barely palpable. Dyspnea, pallor and moderate anemia were noted. The weight on admission was 91 pounds (41.3 Kg.).

The sedimentation rate of erythrocytes was 120 mm. in one hour (Westergren); there were 4,000 to 6,000 leukocytes per cubic millimeter and 2.8 Gm. of albumin and 4.8 Gm. of globulin per 100 cc. of serum. There was albuminuria, grade 2 to 3 (on a grading basis of 1 to 4), with occasional casts and erythrocytes in the urine. The electrocardiogram revealed isoelectric or inverted T waves in leads I, V_1 and V_5 with low amplitude T waves in leads II and III; tachycardia was present. The bone marrow showed the typical Hargraves phenomenon for lupus erythematosus.

Cortisone was administered for 166 days from Feb. 25 through Aug. 9, 1949. The initial doses during the first week were 25 to 50 mg. per day. The only effect noted was a return of the temperature to normal. During the second week, 200 mg. was given daily for three days; then the daily dose was reduced to 100 to 150 mg., and this dose was used throughout the remainder of the course. After the increase in dose, the sedimentation rate dropped from 121 to 61 mm. in one hour (Westergren) in five days. Subsequently it varied between 40 and 60 mm. The patient's appetite and weight gradually improved; the leukocyte count became normal, and the patient became active around the hospital. All symptoms and signs referable to the joints gradually disappeared in one month. The urine continued to show albumin and occasional casts and red blood cells. The bone marrow showed nuclear changes and clumping of polymorphonuclear leukocytes, but on the ninety-second day of treatment with cortisone it showed only an occasional L. E. cell and on the one hundred and fifty-ninth day of

9. Cortisone acetate was supplied by Dr. James M. Carlisle, medical director of Merck & Company, Inc.; ACTH was supplied by Dr. John R. Mote, medical director of The Armour Laboratories.

the course no L. E. cells. Reexamination of the bone marrow one month after the use of cortisone was discontinued showed no L. E. cells but considerable extracellular amorphous material.

During the course, certain physiological effects of the hormone occurred. After about six weeks of treatment, slight edema and fulness of the face were noted. In the eighth week a transitory elevation of blood pressure with headache was present for several days. In the ninth week, the concentration of serum potassium fell to 3.2 milliequivalents per liter and it was necessary to administer potassium chloride. In the tenth week a slight increase was noted in the facial hair.

At the end of the course, Aug. 9, 1949, the patient showed definite signs of hypercortisonism as manifested by full face, increased growth of hair and slight edema. She was afebrile and had no articular symptoms. The sedimentation rate was around 60 mm. in one hour. The value for serum proteins was 6.8 Gm. per 100 cc. with an albumin-globulin ratio of 1:1. The urine still contained albumin and occasional casts and red blood cells.

One month after injections of the cortisone were discontinued, the patient maintained 50 per cent of the improvement in her strength; she had transitory fibrositis but no arthritis.

Ten months after the end of the course of cortisone it was estimated that her disability was about 50 per cent of what it had been previously. She was able to do part of her work at home and care for her child.

Comment.—In this case, when the dosage of cortisone was adequate (1) the signs and symptoms of lupus erythematosus, including the polyarthritis and serous effusions of the pleura and the pericardium, fever and tachycardia, responded promptly and the response was maintained, (2) the sedimentation rate, albuminuria, leukopenia and the albumin-globulin ratio showed improvement, (3) there was a quantitative reduction but not abolition of the L. E. phenomenon in the bone marrow and (4) health improved and there was a prolonged state of relative remission. The typical signs of hypercortisonism which appeared on prolonged administration slowly regressed.

Case 2.—The first suggestion of lupus erythematosus in a college student, 18 years old, was a biologic false positive reaction to a serologic test for syphilis about 20 months before her admission to the clinic. For four months before admission she had had occasional fleeting pains in the thorax and transitory arthralgia of the hands and ankles. Twelve days before admission malaise, fever, vague joint pains, anorexia, occasional vomiting and an erythematous eruption over the medial portions of the cheeks appeared. Examination by her school physician showed enlargement of the cervical lymph nodes and leukopenia. The past history revealed that at the age of 12 years she had had an abnormal guilt reaction and that six months before her admission to the clinic there had been a recurrence of compulsive guilt feelings which had required psychiatric management.

Examination on admission, on Oct. 23, 1949, showed moderate fever and mild erythema over the nose and medial portions of the cheeks. The lips were cracked and crusted, and there were hemorrhagic erosions on the soft palate, a mild systolic murmur at the pulmonic area and apex and slight generalized enlargement of the lymph nodes. Laboratory examinations revealed leukopenia (1,700 to 2,000 leukocytes), thrombocytopenia (58,000 thrombocytes), increased sedimentation rate (80 mm. [Westergren]), an albumin-globulin ratio of 3.3:3.4 and albuminuria, grade 2. Culture of the urine showed Escherichia coli. The sternal marrow was positive for the L. E. cells but not strongly so. Flocculation tests were positive for syphilis; the Kolmer-Wassermann reaction was anticomplementary.

During the patient's first week in the hospital, the fever increased to 104 F., prostration was more pronounced, facial edema was noted, anorexia was severe and there was occasional vomiting.

Cortisone was administered for 21 days, beginning Nov. 2, 1949; a total of 3,800 mg. was given (fig. 1). On the first day the dose was 200 mg., and for each of the next four days it was 100 mg. In spite of this level, the patient became more critically ill and the leukoctye count decreased, once reaching 1,200 cells per cubic millimeter. The dose of cortisone

was increased to 200 mg. daily. During the next six days the temperature descended gradually to normal, and within 10 days the facial edema and erythema had subsided. The patient's general condition and appetite improved steadily, and the patient eventually felt normal except for weakness. The leukocyte count returned to normal by the fifth day of dosage with the increased amount. Near the end of the 21 day course, the bone marrow no longer showed the L. E. cells in typical form, although an excess of amorphous material was noted.

Three days before the end of the course the patient's previously experienced compulsive guilt feelings recurred and progressed rapidly to a point where transfer to a psychiatric ward was necessary.

During the subsequent five weeks in the hospital, the mental symptoms gradually cleared and the patient's general condition remained good. Albumin gradually disappeared from the

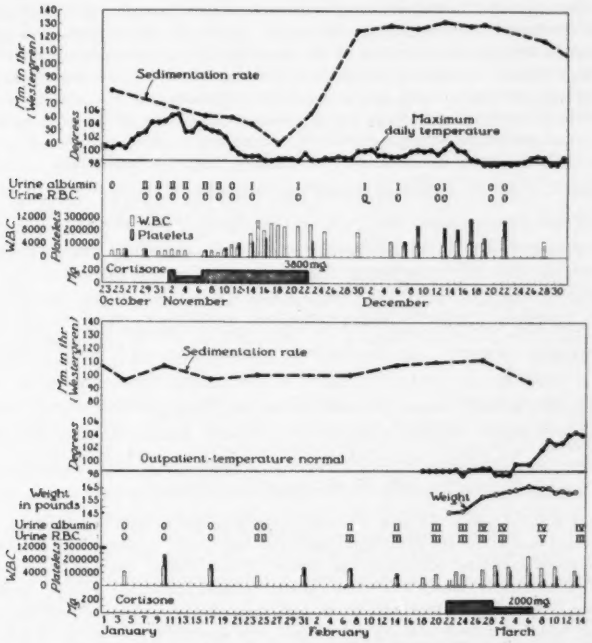

Fig. 1 (case 2).—Data on sedimentation rate and temperature as well as urinary observations and levels of leukocytes and platelets. A gain in weight (edema) during the second course of cortisone may be noted. The patient died on March 14, 1950.

urine, and the albumin-globulin ratio and the platelet counts returned to normal. The elevated sedimentation rate (118 to 130 mm.) and the moderate anemia persisted. In the next three and one-half weeks, during which the girl was an outpatient with limited activity, there was no essential change in her physical condition. Moderate fatigue continued. The results of laboratory tests remained unchanged.

About four weeks after her dismissal from the hospital and two months after the end of the first course of cortisone, the urine began to show erythrocytes and then albumin. Soon a slight facial erythema and slight evening fever appeared. The sternal marrow again showed L. E. cells, and leukopenia was present.

A second course of cortisone was given for 13 days beginning Feb. 22, 1950. The patient was on an outpatient status during this course. The dose was 200 mg. daily for seven days, and then 100 mg. daily for six days, for a total of 2,000 mg. The facial erythema

and the fever disappeared, and the leukocyte count returned to normal. The urinary changes, however, became more pronounced, until albuminuria of grade 4 with gross hematuria was present. The urinary excretion of protein in 24 hours was 7.67 Gm. on the twelfth day of the course and 9.8 Gm. three days later, on the second day after the end of the course. During the course there was a rapid increase in body weight amounting to 20 pounds (9.1 Kg.) due to the retention of fluid. Tests for urea, sodium, potassium, sulfates and carbon dioxide in the blood and serum all showed normal conditions.

The patient was readmitted to the hospital two days after the last injection of cortisone. The edema could not be reduced; pleural effusion, pulmonary edema and increasing fever supervened, and she died on the sixth day after admission.

Necropsy observations were bilateral hydrothorax (2,000 cc. of fluid on each side) with anasarca, grade 3, especially of the trunk; hydropericardium (300 cc. of fluid); bilateral pulmonary edema, grade 3, with beginning bronchopneumonia; atrophy of the adrenal glands; petechiae of the brain; hypertrophy of the spleen; edema of the kidneys, and nonbacterial vegetative endocarditis on all the valves of the heart and the mural endocardium. Microscopically, the wire looping of the basement membrane of the glomeruli of the kidneys typical of lupus erythematosus was present, as well as the onion skin lamellation of the vessels of the spleen and lymph nodes. In the adrenals there was a widening of the zona glomerulosa with encroachment on the zona fasciculata, which contained only a small amount of fat. The zona reticularis was widened. The evidence indicated that the adrenal gland was functioning.

Comment.—This case demonstrated the following factors: 1. Large doses of cortisone were needed during the early, acute phase of the disease. 2. The symptomatic response of the fever, arthralgia and facial erythema was maintained for almost two months after cortisone was received for 21 days. 3. In spite of improvement in physical well-being, except for the return to normal of the leukocyte count and the lessened albuminuria the fundamental laboratory features of the disease were not affected. 4. Hematuria, albuminuria and fever were the first evidences of relapse. 5. Cortisone flared a preexisting psychotic state. 6. Cortisone, during the second period of administration, brought about a gradual retention of salt and water which, with the progressive renal damage, led to a fatal termination. 7. Necropsy revealed massive edema and typical signs of lupus erythematosus disseminatus with nonbacterial endocarditis.

CASE 3.—A girl, 17 years old, was admitted directly to the hospital on Sept. 27, 1949. For one year she had had recurrent arthralgia associated with mild soreness in the throat. Two and one-half months before admission the joints of the fingers became more tender and painful, and subsequently numerous other joints became painful. Fever, weakness and anorexia began two weeks before admission, and facial erythema was noted about 10 days later. By the time the patient entered the hospital, her condition was worse, her temperature was rising and she was vomiting frequently. Six months previous to the onset of the present illness, she had had hives for a few days, one week after receiving a single injection of antitoxin for suspected diphtheria.

Examination revealed fever ranging from 100 to 105 F.; well delineated erythema on the eyelids, forehead and medial portions of the cheeks; erosions on the buccal mucosa, and the presence of a palpable spleen. Leukopenia (3,000 leukocytes), increased sedimentation rate (50 mm. [Westergren]) and an albumin-globulin ratio of 2.5:2.6 were noted. Albuminuria was graded 1 to 2. The bone marrow contained many typical L. E. cells.

The patient was treated with ACTH for 47 days, beginning Oct. 3, 1949. The initial daily dose of 80 mg. (in four injections per day) produced a dramatic drop in temperature to normal within 24 hours. The articular pains disappeared in 48 hours, and the vomiting, anorexia and malaise disappeared soon thereafter. The cutaneous lesions faded steadily and were no longer discernible after nine days except as a faint brownish stain. The sedimentation rate dropped to 27 mm., and the leukocyte count rose to between 5,000 and 6,000. Albuminuria, grade 1, persisted. During the first two weeks of the course of ACTH there were transient episodes of apprehension and some insomnia but no other toxic manifestations.

On the twelfth day after administration of ACTH was begun the patient had sudden pain in the lower part of the abdomen. This was not considered by the surgical consultant to be typical of appendicitis, and surgical intervention was deferred. Tenderness developed in the abdomen and persisted during the next week, when there was a sudden exacerbation, followed in the next 48 hours by signs of peritonitis. Emergency laparotomy performed on October 23 revealed purulent peritonitis with pelvic abscesses. The appendix was normal; intestinal perforation was suspected but could not be found. In spite of a condition of severe shock prior to and incident to surgery, the patient survived the operation with the aid of blood transfusions and increased doses of ACTH.

After operation, administration of ACTH was continued but the dose was reduced gradually. A decrease in the level of potassium in the blood required the administration, at first by vein and later by mouth, of potassium chloride in doses up to 12 Gm. daily. Between the eighth and twelfth postoperative days the patient had episodes of sudden thoracic pain, cortical blindness and several convulsive seizures. The dose of ACTH was increased for several days, then reduced and stopped first on November 13, 21 days after the operation. Immediately after cessation of this therapy fever accompanied with sensations of dyspnea, anxiety and restlessness developed. ACTH was given again, after an interval of two days, for four days, with some general improvement and suppression of fever. Its use was stopped on November 20. After discontinuance of its use, the fever, as well as the previous symptoms of dyspnea and apprehensiveness, again returned.

On November 22 a course of cortisone was started (the supply of ACTH being exhausted); 300 mg. was given the first day, and then 200 mg. daily. Again there was a suppression of fever. By December 7 it was apparant that an abscess had formed under the diaphragm; 1,000 cc. of pus was evacuated surgically, and the patient's condition improved. On December 12, after 21 days of treatment with cortisone, use of the hormone was discontinued. At this time slight fulness of the face and a few comedos on the forehead were noted. Fever again developed the day after the last injection of cortisone. On November 20 another subphrenic abscess was drained surgically, and on December 26 an abscess drained spontaneously through the lower end of one of the abdominal incisions; this development led to a persistent fecal fistula.

At no time after the initial response to ACTH was there any renewal of the recognizable signs of lupus erythematosus. There was fever, which was suppressed by ACTH and cortisone but was apparently due to the presence of multiple peritoneal abscesses. The sedimentation rate became more elevated with the development of peritonitis and remained so. The level of serum globulin remained equal to or higher than that of serum albumin throughout the entire hospital stay. The bone marrow on November 28 (on the sixth day of the course of cortisone) showed no typical L. E. cells, but there was increased clumping of leukocytes. The electrolyte balance was seriously disturbed during the course of ACTH, especially while the patient was unable to eat. The notable features of this disturbance were low levels of potassium and of chlorides in the blood.

The patient's course subsequent to her treatment with cortisone was a gradual downhill one. Pus continued to drain from the operative incisions; a fecal fistula developed, and anorexia was severe. Organisms cultured from the wounds were Escherichia coli and a Proteus; these were highly resistant, in sensitivity tests, to aureomycin, streptomycin, chloramphenicol (chloromycetin®) and terramycin. None of these antibiotics seemed to have any effect on the condition. The patient slowly failed and died March 26, 1950, six months after admission. During the latter weeks of her illness, no signs of lupus erythematosus were apparent.

At necropsy minimal evidence was obtained of the usual signs of lupus erythematosus. Throughout the entire peritoneal cavity fine fibrous adhesions bound all the structures. The pelvic organs were bound in a mass of hemorrhagic fibrous adhesions. There were pleuritic adhesions but no signs of old pericarditis and no evidence of vegetative endocarditis. The liver was fatty; the adrenal glands appeared normal except for a slight decrease in the lipid content. There was emaciation, and death was due to inanition.

Comment.—This case demonstrated (1) prompt symptomatic control of the surface features of lupus erythematosus on the administration of ACTH and, later, cortisone; (2) the suppressive effect of these hormones on the symptoms of com-

plicating infection, such as peritonitis and the development of multiple abscesses, and the supportive influence of these hormones on the shock of infection and extensive surgical procedures; (3) the lack of interference with wound healing during the period of administration; (4) the development of signs of disturbed behavior and of convulsions, a feature due to the lupus erythematosus, the complicating infection or the hormones; (5) mild signs of hypercortisonism which were transient; (6) the persistence of the L. E. phenomenon in the bone marrow, and (7) death from chronic infection and inanition with little residue of lupus erythematosus in the observations at necropsy.

CASE 4.—A housewife, 45 years old, gave a history of recurring pain involving numerous joints for 15 or 20 years. In 1943, when she first sought medical aid, she received a series of streptococcic vaccine injections. After this treatment she was free of symptoms for three years. In the fall of 1945 she first noted an indolent red plaque on the right cheek; this condition spread to the nose and left cheek in 1947, after the use of ultraviolet radiation. At this time a diagnosis of discoid lupus erythematosus was made. In December 1947 the patient first came to the clinic and the diagnosis was confirmed. The sedimentation rate was 50 mm. (Westergren); the leukocyte count was normal, and there was albuminuria, grade 1. The patient returned home and was given vitamin E by mouth and by injection.

In 1948, her gallbladder was removed by her home physician because of abdominal pain and stones in the gallbladder. In the spring of 1949 the articular pain became worse and the patient became very tired, so that she had to spend part of the time in bed.

In July 1949 she returned to the clinic; the skin lesions were present over the face, arms and upper part of the back. The sedimentation rate was 107 mm., and the leukocyte count, 5,000, and there was albuminuria, grade 1.

After her return home the patient stayed in bed for one month and thereafter felt better for a while. In November 1949 fever, cough and further extension of the skin lesions occurred. The patient was hospitalized and given penicillin with little benefit. On Nov. 28, 1949, she was transferred to the clinic and immediately entered the hospital.

Her temperature on admission was 100 to 101 F.; she was uncomfortable, weak and exhausted, and she coughed frequently. The skin showed mottled erythematous atrophic patches in widespread distribution including the nose and cheeks, the chin, the upper part of the back, arms, palms, finger tips, buttocks and soles of the feet. There were hemorrhagic crusts on the lips and shallow erosions on the oral mucous membranes. An adenoma measuring 4 cm. in diameter was found in the thyroid gland. The blood pressure was 144 mm. of mercury systolic and 90 mm. diastolic. The remainder of the physical examination revealed no abnormality.

Results of laboratory examinations were as follows: sedimentation rate, 71 mm. (Westergren); leukocyte count, 3,300; 10.4 Gm. of hemoglobin per 100 cc., and 5.8 Gm. of total serum proteins per 100 cc., with 2.9 Gm. of albumin and 2.9 Gm. of globulin. The platelet count was 70,000 as determined by the direct method. There was albuminuria, grade 2. Examination of the bone marrow showed L. E. cells.

During the first month in the hospital, the patient was treated with blood and plasma and injections of testosterone. In spite of these and other supportive measures, her condition became worse. The skin lesions became more widespread, and many of the lesions became eroded and crusted, especially on the upper part of the arms, and tenderness was a prominent symptom. The temperature increased to between 101 and 102 F. The sedimentation rate ranged between 66 and 85 mm., and the leukocyte count varied from 2,900 to 6,200 with no definite trend. The level of serum proteins fell to 5.4 Gm. per 100 cc. with 2.2 Gm. of albumin and 3.2 Gm. of globulin. Albuminuria, grade 2, continued.

Cortisone was administered for seven days beginning Dec. 29, 1949; a total of 1,300 mg. was given. During the course there was a slight drop in temperature. Improvement in the skin lesions was first noted in four or five days. The patient became apprehensive, restless and anxious and was confused at times. A tremor developed. These symptoms plus an increase in the blood pressure to 180 mm. systolic and 120 mm. diastolic on the seventh day led to the withdrawal of the hormone. The leukocyte count was not affected; the sedimentation

rate, measured once during the course, was higher (100 mm.). The blood urea level was elevated transiently during the first few days of the course.

During the next 30 days the patient received no cortisone. The skin continued to improve, and two and one-half weeks after the end of the course the eroded areas were healed and the erythema was much diminished. In less than a week more, the erythema began to increase again and tenderness of the skin rapidly returned. An abscess of the buttocks required surgical drainage 12 days after the end of the course of cortisone. By the end of the 30 day interval, the patient was again quite ill, toxemic and apprehensive; fever was increasing and did not respond to the administration of penicillin (fig. 2). Albuminuria persisted; the the sedimentation rate was between 60 and 90 mm., and the leukocyte count gradually dropped to less than 4,000.

A second course of cortisone was started Feb. 4, 1950. A dose of 300 mg. was given the first day, 200 mg. daily for the next four days and then 100 mg. daily for nine days, for a total of 2,000 mg. in 14 days. The temperature reached normal by the third day of cortisone therapy, and the patient's general condition and appetite improved steadily. The cutaneous plaques began to subside within a few days. The sedimentation rate increased slightly during the course; the leukocyte count increased to normal levels. The concentration of urea in the blood rose temporarily to 66 mg. per 100 cc. on the sixth day but was normal thereafter. The values for hemoglobin and serum proteins dropped slightly. The levels of carbon dioxide,

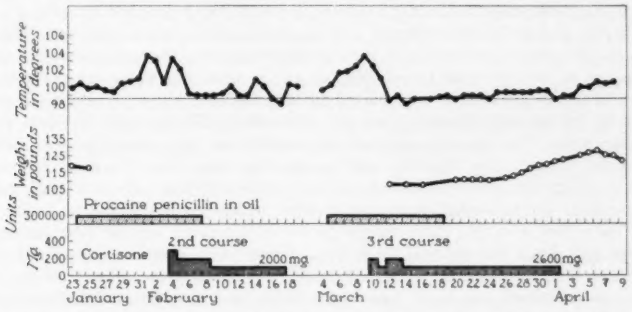

Fig. 2 (case 4).—Data on temperature and weight, showing a drop in fever during cortisone therapy after a lack of effect of the administration of penicillin. Note the gain in weight (edema) toward the end of the third course of cortisone.

chlorides, sodium and potassium in the blood were unaffected. The albuminuria, grade 2, was unchanged.

An interval of 20 days elapsed after the second course of cortisone. The sequence of events was much as after the first course, with improvement in the skin for about one week but a gradual relapse thereafter so that by 15 days after the end of the course the eruption was as intense and widespread as ever and superficial erosions again appeared. The bone marrow showed many L. E. cells 18 days after the end of the second course.

A third course of cortisone was given between March 10 and April 1, 1950. The dosage was 200 mg. daily for three of the first four days (fig. 2) and on other days 100 mg. daily, for a total of 2,600 mg. in 23 days. Again the temperature, the skin lesions and the general condition of the patient improved. The appetite increased to the point that the patient was ravenous. Pronounced euphoria and exhilaration occurred toward the end of the course. Strength improved so much that the patient was able to walk in the hall. Beginning about the seventeenth day, an increase in weight was noted. By the twenty-third day, when use of the cortisone was discontinued, the patient had gained 12 pounds (5.4 Kg.), and 6 additional pounds (2.7 Kg.) were added during the next five days. The sedimentation rate had decreased from previous levels of 128 mm. to 53 mm., two days after the end of the course. The leukocyte count fluctuated but tended to be slightly higher. The value for hemoglobin increased by about 1.5 Gm. per 100 cc. There was a slight reduction in the total serum proteins, mainly at the expense of

the globulin. The albumin-globulin ratio just after the course was 2.0:2.6. The value for blood urea increased transiently to 51 mg. per 100 cc. early in the course. The blood levels of potassium and carbon dioxide were unchanged during the course. Albuminuria continued as grade 2 early in the course and became grade 3 toward the end, when retention of fluid and relative oliguria occurred.

After the end of the third course of cortisone on April 1, 1950, an interval of 40 days elapsed before the next period of administration. More than half of the previously noted gain of 18 pounds was lost in the five days after the highest weight was recorded, and the remainder during the next 12 days. Two abscesses characterized by relatively little inflammatory reaction developed on the right thigh and right buttock and required surgical drainage on the ninth day. Fever was again present from the seventeenth day, the temperature ranging from 100 to 102 F. The skin maintained its improvement for at least 18 days and then slowly became more erythematous but not with the rapidity or extent noted after the first two courses of cortisone. The euphoria gradually subsided and was replaced by an increasing apathy. The appetite failed, and vomiting became a prominent symptom after the third week. Thoracic pain and cough also returned and became so severe that digitalization and oxygen therapy were instituted on the thirty-eighth day. Edema was present to a slight degree. The patient's condition became critical; there was no response to treatment with penicillin, and administration of cortisone was resumed on the forty-first day after the end of the third course. During the time that the patient's condition was becoming progressively worse, the sedimentation rate increased to its earlier high levels, the leukocyte count ranged from 4,000 to 6,000, the concentration of serum globulin slowly increased and the albuminuria, grade 2, persisted. Many L. E. cells were found in the bone marrow on the eighteenth day after the last injection of cortisone. During the course of the febrile illness, alopecia of the scalp hair developed gradually.

The fourth course of cortisone was started on May 12, 1950, when the patient was critically ill. A dose of 300 mg. was given the first day, followed by 200 mg. daily for three days, and then 100 mg. daily. The patient's condition was complicated by a convulsion on the evening of the first day of the course, and two more on the following day. The temperature became normal on the fourth day and elevated 1 degree (F.) on the fifth day. Mersalyl (salyrgan®) was given on the third day to combat edema, but its administration was followed by anuria. Three days later the patient went into status epilepticus for several hours, and the fever and pulse rate increased to high levels for the next three days. Some improvement in the general condition occurred thereafter. Chemical constituents of the blood changed as follows: 48 mg. of urea per 100 cc. on the second day to 90 mg. on the eighth day; 3.1 milliequivalents of potassium per liter on the second day, 2.8 milliequivalents on the fourth day and an increase to 3.5 milliequivalents on the eighth day, after intravenous administration of potassium chloride with the fluids that the patient required. At this writing (June 1, 1950) she is able to take nourishment by mouth, but her consciousness is clouded, she is disoriented and there is weakness of the left side.

Comment.—This case demonstrated (1) favorable but temporary benefit in the acute phases of lupus erythematosus during each of four periods of the administration of cortisone; (2) relapse in 21, 10 and 19 days, respectively, after each course completed; (3) healing of eroded cutaneous plaques of lupus erythematosus as well as satisfactory response to surgical drainage of several subcutaneous abscesses while the patient was responding to treatment with cortisone; (4) lack of significant change in the fundamental abnormalities of the disease as determined by laboratory studies in spite of clinical improvement; (5) the persistence of the L. E. phenomenon in the bone marrow; (6) unfavorable effects of cortisone in the form of (*a*) swings of mood from anxiety to euphoria with bulimia and, later, depression, (*b*) temporary hypertension and (*c*) a rapid accumulation of interstitial edema with retention of sodium and chloride during the third course with subsequent spontaneous diuresis, and (7) a dramatic interruption of a seemingly terminal phase, including convulsive features, at the end of six months of observation.

CASE 5.—A 26 year old woman was first seen in the clinic on June 14, 1949. Five months earlier she had had an infection of the ear, which was treated with a sulfonamide. For four months before admission, she had had stiffness and slight swelling in multiple joints and an occasional pleural type of pain. Malaise and fatigue had been present for less than one month, and an erythematous rash on the face, neck and arms had been noted a few days. A diagnosis of disseminated lupus erythematosus was made on the basis of the clinical observations plus leukopenia, anemia, increased sedimentation rate and the presence of the L. E. phenomenon in the bone marrow. The patient returned home but in a short time became acutely ill with high fever, increased joint pains and increased erythema of the face. She returned July 7, 1949, for hospitalization.

During one month in the hospital she remained acutely ill, with a temperature range from 103 to 105 F., a pulse rate between 110 and 130 beats per minute, toxemia and a persistent cough. The facial erythema was intense, and there were bilateral severe subconjunctival hemorrhages. Supportive measures including five transfusions with administration of a total of 2,000 cc. of blood were of moderate benefit.

During the next two months at home, her condition gradually shifted from an acute to a subacute state, with pronounced loss of weight, anemia, decubitus ulcers and a lower but persistent fever.

The patient was readmitted to the hospital on Oct. 7, 1949, showing decided physical deterioration as compared to her status when first seen. The temperature was 100 to 102 F., and she was emaciated, anemic and weak. A large decubitus ulcer was present over the sacrum, with smaller ones over the heels, and another ulcer, possibly embolic in origin, was present on the posterolateral aspect of the lower third of the right leg. The previous erythema of the face was replaced by slight atrophy and pigmentation of the skin. The joints of the fingers and wrists showed tenderness and swelling, grade 1 to 2. The sedimentation rate was 114 mm. (Westergren); the leukocyte count, 4,500; the value for hemoglobin, 8.6 Gm. per 100 cc.; the serum albumin-globulin ratio, 1.5 : 3.3, and albuminuria, grade 3.

The patient received three courses of cortisone. The first two were identical, with 100 mg. being given daily for 14 days. In the third course cortisone was given at the rate of 200 mg. daily for a total of 14 days plus a last dose of 100 mg. on the fifteenth day. The total dose during this course was 2,900 mg.

During the first course, October 15 through 28, the temperature returned to normal in four days, the swelling and tenderness of the joints began to decrease on the fifth day and the decrease slowly continued until 75 per cent improvement was present by the end of the course. On the ninth day of administration, there was a brief generalized convulsion (the only such occurrence). The appetite and well-being improved. The sedimentation rate decreased to 88 mm., and the amount of urinary albumin was slightly reduced. Other laboratory data remained unchanged.

The interval between the first and second courses was 12 days. After about seven days of slight tenderness of joints, anorexia, malaise and low grade fever returned.

During the second course, November 10 through 23, the temperature promptly became normal, the tenderness of the joints diminished and the appetite improved but the response was not quite as good as with the first course. No significant changes were noted on laboratory tests.

The interval between the second and third courses was 13 days. There was again some return of fever and articular tenderness and a general loss of ground. The sedimentation rate increased to 154 mm. on one occasion.

The last course of cortisone was given from December 7 through 21. With the larger dose of 200 mg. daily, there was a more brisk and more complete response in the articular tenderness; the fever disappeared, and appetite and sense of well-being improved. The weight rose rapidly during the last half of the course because of retention of fluid; the increase amounted to 20 pounds (9.1 Kg.). Cellulitis developed in one buttock during this course, and an abscess formed which required surgical drainage. There was a decrease in the sedimentation rate to 93 mm. on the thirteenth day of the course, and the hemoglobin increased about 1.0 Gm. per 100 cc.

Observation after the last course showed a return of fever, with temperatures of 100 to 101 F. The retained fluid was lost, with the weight diminishing most rapidly between the sixth and tenth days after the last injection of cortisone, but the previous level of weight was not reached until the seventeenth day. The tenderness of joints did not recur for about two weeks

and was not severe. The sedimentation rate increased slightly, and after one month the leukocyte count dropped to 3,100. The ulcers on the heels and right leg healed during the period of hospitalization at about the normal rate. The ulcer over the sacrum was cleaner and diminished to about half its original size. At the time of dismissal, appraisal of the end result was that slight over-all gain had been achieved.

Reexamination three months later (four and one-half months after the last course of cortisone) showed a temperature of 101 to 102 F., some deterioration in the general physical status with persistence of the articular tenderness in the fingers and wrists and no fundamental change in the laboratory observations.

Comment.—This case demonstrated the influence of cortisone on lupus erythematosus in somewhat less than the acute phase of the disease: (1) an initial arrest of the downhill course at the time of admission, (2) prompt relief of the presenting symptoms of arthritis and fever with improved appetite and sense of well-being during each of the three periods in which the hormone was administered, (3) some improvement in anemia but no change otherwise in the fundamental laboratory aspects of the disease, (4) progressive healing of cutaneous ulceration, (5) relapse of symptoms in seven to 10 days after withdrawal of the hormone, (6) temporary gain in weight due to retention of fluid during the third period of administration, when the daily dose was 200 mg., and (7) a slow progressive decline in general health and in the state of the lupus erythematosus during the three months of observation subsequent to the third course.

CASE 6.—The patient, a girl 15 years of age, was admitted directly to the hospital on Feb. 2, 1950. She had had many episodes of infection involving the ears, mastoids, throat and kidneys, the first having occurred when she was 2½ years old. Sulfonamides and penicillin had provoked urticarial reactions. For eight years she had spent several weeks in bed each year because of recurrent articular pain, fever and elevation of the sedimentation rate. Rheumatic fever had been diagnosed during the first such episode, when a heart murmur was heard. In the summer of 1949 she took frequent sunbaths without apparent reaction. In October 1949, four months before admission, she had had generalized aching and fever, and she had been in bed from that time on. Three weeks before admission she had had increased fever and an erythematous eruption on the cheeks. For five days she had had pleuritic pain in both shoulders and occasional vomiting.

Examination showed a moderately ill, thin girl, whose temperature was 101.6 F. There was a bright erythema in a butterfly distribution over the middle of the face and several erythematous macules over the outer aspect of the upper part of each arm. Small cervical and axillary lymph nodes were palpable. The heart was not enlarged, but a prominent harsh systolic murmur was heard at the apex. Dulness and diminution of breath sounds were noted over the base of the left lung. The joints were not tender or swollen. Laboratory examinations showed a sedimentation rate of 90 mm. (Westergren), 2,400 leukocytes, 58,000 platelets, 9.7 Gm. of hemoglobin per 100 cc., an albumin-globulin ratio of 3.0:3.1 and albuminuria (grade 2), red blood cells and granular and hyaline casts in urine. The bone marrow showed the presence of the L. E. phenomenon.

During the first five days in the hospital the patient lost ground. The temperature remained elevated; she vomited frequently, and pain, tenderness and rigidity of the abdomen, which raised the question of peritonitis, developed. She was listless and appeared acutely ill.

Administration of cortisone was begun on February 7, the sixth hospital day, with a dose of 300 mg. During the next four days the dose was 200 mg. daily, and thereafter for 16 days, 100 mg. daily. The total amount given in 21 days was 2,700 mg. (fig. 3).

Within 24 hours of the beginning of the course the temperature dropped to normal, the abdomen became softer and less tender and the patient's general condition improved. In another 24 hours the abdomen was apparently normal. A reduction in the facial erythema was noted on the third day of treatment with cortisone; by the seventh day it was reduced by about 75 per cent, and by the twenty-first day there remained only a faintly perceptible blush, which soon

disappeared entirely. The patient's general condition continued to improve; the appetite increased to more than normal, and she had a sense of well-being. During the latter half of the course she gained 17 pounds (7.7 Kg.). Half of this was lost by diuresis by the fourth day after the end of the course of cortisone, and the remainder by the twelfth day. Slight peripheral edema was noted during the last few days of the course. On the last two days, the patient complained of difficult breathing and transient orthopnea. A roentgenogram of the chest showed a slight increase in the size of the heart shadow.

On the seventh day of the course of cortisone the leukocyte count had increased to normal, and frequent subsequent counts were normal. The cortisone therapy had no effect on the sedimentation rate, hemoglobin, serum proteins or platelet count. The concentration of serum potassium was slightly lowered by the end of the course to 3.4 milliequivalents per liter, as compared to an initial level of 4.9 Albuminuria increased from grade 2 to 3. The L. E. phenomenon was still present in the sternal marrow on the fifteenth day of cortisone.

No cortisone was given from February 28 to March 15. About March 10, the patient began to complain of transient dyspnea and pleural pain appeared over the left shoulder and scapular region. The appetite became poor; the temperature and pulse rate increased. Rales were heard occasionally in the bases of the lungs. There was no return of facial erythema. Laboratory

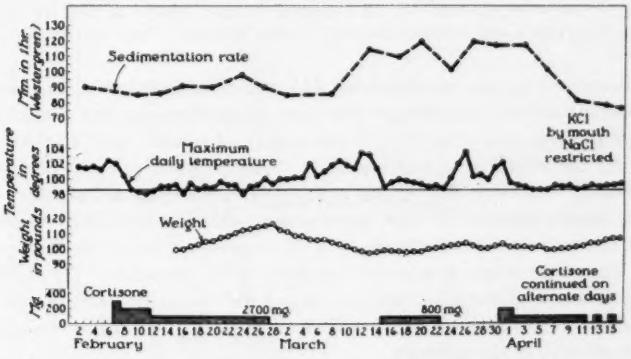

Fig. 3 (case 6).—Data on sedimentation rate, temperature and weight, showing the response of fever during cortisone therapy. The patient died on June 1, 1950.

observations remained essentially unchanged except for albuminuria, grade 4, on one occasion and the discovery of hematuria on microscopic examination on two occasions.

On March 15 the second course of cortisone was started, 100 mg. being given daily for eight days. During this course, the temperature dropped to levels averaging 99.5 F. and the pulse rate diminished but there was little effect on the patient's sense of well-being, appetite or thoracic pain. On the seventh day of the course, a pleural friction rub was heard in the base of the left lung. The patient gained 6 pounds (2.7 Kg.); the maximal weight was reached on the fourth day after administration of cortisone was discontinued. In the next two days, she lost 3½ pounds (1.6 Kg.).

During the eight day interval after cortisone, the temperature rose to 102 to 103.6 F. for two days and later dropped to 100 to 102 F. The general condition remained about the same. Striae were noted on the lateral portions of the hips for the first time. A roentgenogram of the thorax showed further enlargement of the heart. There were hematuria and pronounced albuminuria. No significant changes were noted on other laboratory examinations.

A third course of cortisone was started on March 31; 200 mg. was given daily for the first two days, 100 mg. daily for the next 10 days, and then 75 to 100 mg. every second day for a period of more than seven weeks. The temperature again dropped to normal in 24 hours and remained down. General well-being and thoracic pain did not improve much if any. Various areas, such as the knees, wrists, elbows and abdomen, were described as tender and painful

at irregular times. The appetite was only fair. Between the tenth and eighteenth days of treatment with cortisone, the patient gained 7½ pounds (3.4 Kg.) and the concentration of potassium fell to 3.0 milliequivalents per liter of blood. At this point (April 18) daily doses of 4 Gm. of potassium chloride were started. The weight dropped 4 pounds (1.8 Kg.) in the next three days and another 3 pounds (1.4 Kg.) in the next five days and thereafter remained fairly constant. The level of potassium rose to 4.1 milliequivalents two days after administration of the potassium chloride was started and was 4.6 milliequivalents four days later.

As the course lengthened the patient slowly lost ground, and by the fiftieth day (May 19) she was extremely listless and weak and had no appetite. The level of hemoglobin was 8.6 Gm. per 100 cc. Thoracic pain was variable but often severe. Various joints were tender at times. Slight fever (temperature of 100 F.) developed. The sedimentation rate fluctuated between 60 and 135 mm. without apparent relation to the clinical condition. On the fifty-third day a sharp rise in fever occurred, with an aggravation of pleural pain and signs of pulmonary involvement. The administration of aureomycin by mouth served to bring the temperature to normal, but the general condition remained critical. Albuminuria of severe degree persisted, and the laboratory data otherwise indicated a grave prognosis.

Note.—The patient died on June 1 in shock after two days of abdominal distress. Postmortem examination revealed signs of acute hemorrhagic pancreatitis as the immediate cause of death. There were also signs of old rheumatic valvular disease as well as nonbacterial vegetative endocarditis and fibrinous pericarditis with effusion. There was gross atrophy of the adrenals.

Comment.—This case demonstrated (1) symptomatic improvement under cortisone therapy initially but relapse when use of the hormone was discontinued or the quantity given was reduced, (2) persistence of pleural pain, (3) retention of fluid under the intensive administration of cortisone when salt was not restricted, (4) gradually increasing albuminuria and persistence of original laboratory features of lupus erythematosus, (5) the development of striae and (6) a slowly progressive decline in general health in spite of suppression of surface features of the disease while the patient was under treatment with cortisone. Terminally there were found acute hemorrhagic pancreatitis and old rheumatic heart disease as well as characteristic pathological signs of disseminated lupus erythematosus and postcortisone atrophy of the adrenals.

Case 7.—A woman 20 years old had had influenza two years before admission, with slow recovery. Five months before admission arthralgia had appeared; it had gradually progressed into arthritis, and the patient had considerable disability in the hands. Thoracic pain had been present occasionally for three months, a slight facial erythema for six weeks and pronounced fatigue and fever for three weeks before she was first seen by us, on Feb. 9, 1950.

On admission there were moderate fever, a temperature up to 103 F., erythema over the cheeks and nose and arthritis with limited motion in the fingers and hands and with involvement of other joints, notably the left knee, where effusion was present. A faint systolic murmur was heard in the aortic area and along the left sternal border. There were leukopenia (3,600 leukocytes per cubic millimeter of blood), a rapid sedimentation rate (110 mm. Westergren), an albumin-globulin ratio of 2.9:4.3 and albuminuria, grade 3. The bone marrow showed the presence of the characteristic L. E. phenomenon.

The first course of cortisone, 200 mg. daily, was begun Feb. 20, 1950, and produced prompt and eventually complete clearing of the articular symptoms and objective observations. The temperature subsided to normal in 24 hours, but after two and one-half days at normal levels, there was a sudden elevation of temperature due to pneumococcic septicemia (fig. 4). After the initial spiking, penicillin was administered and the temperature remained between 100 and 101 F. in spite of negative blood cultures. There was considerable improvement in the appetite and well-being. The value for serum potassium fell to 2.8 milliequivalents per liter, and the initial leukopenia improved, but no other significant changes occurred in the laboratory observations.

Use of cortisone was discontinued after 10 days and a total dosage of 1,800 mg. because of the development of symptoms of mental depression and brief periods of hysterical anxiety. There had been a loss of 8 pounds (3.6 Kg.).

The interval of 14 days between the first and second courses was marked by a return of slight stiffness and soreness in the hands and wrists, in eight days, and a gradual return of leukopenia. The low grade fever persisted.

In the second course of cortisone, of nine days' duration, beginning March 16, the patient received a total of 1,200 mg. Within three days, the temperature returned to normal and there was a rapid improvement in joint symptoms, the appetite increased and the patient felt better. The abnormalities of laboratory observations persisted except that leukopenia was less pronounced during the period of administration of cortisone.

The next interval without cortisone was of 13 days' duration. A slight fever of 1 to 1.5 F. reappeared on the twelfth day. Vague chest pains were present at times, and slight articular pain and tenderness in one finger and slight facial erythema returned in about 12 days.

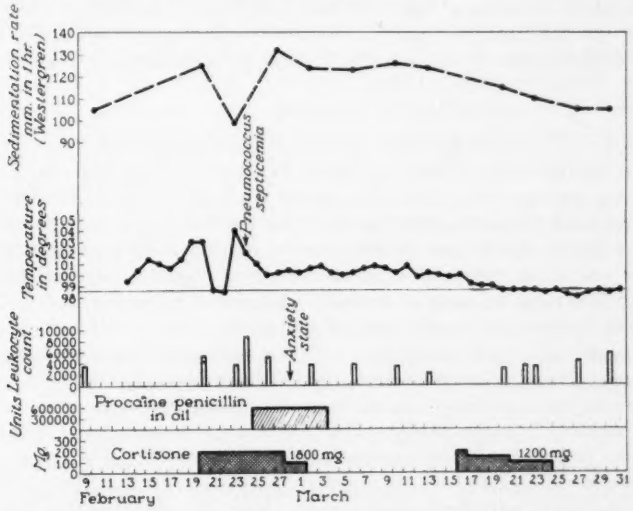

Fig. 4 (case 7).—Data on sedimentation rate, temperature and leukocyte counts. The systemic reaction of septicemia was somewhat subdued by the action of cortisone.

The third course of cortisone was started April 7; a dose of 100 mg. was given daily during the first week, and then on alternate days. The dose on the days cortisone was given was gradually cut to 75 mg., and then to 50 mg. for the next 12 days. Subsequently 100 mg. and also 75 mg. on alternate days were used for varying periods. At the time of writing, the course had been carried on for 55 days.

As in the first two courses, there was a prompt initial improvement when 100 mg. was given daily. Later adjustments in dosage showed that 75 mg. on alternate days failed to prevent joint soreness, especially in the fingers, and that with the use of this amount slight facial erythema returned. A fulness of the face became noticeable, and this has persisted. For several weeks 100 mg. was given on alternate days.

The elevation of the sedimentation rate, the reversal of the albumin-globulin ratio and the presence of albuminuria were unaffected by treatment with cortisone either in the short courses of intensive doses or in the longer course of lower doses. The hemoglobin level improved slightly during the long course, probably as a result of better intake of food. During the third course the dietary intake of salt was restricted; no edema and no gain

in weight occurred. There was a gradual increase in albuminuria, and the level of serum globulin reached 5.1 mg. per 100 cc. A second examination of the sternal marrow, during the third course, three months after the initial marrow examination, still showed the presence of the characteristic L. E. phenomenon.

Comment.—This case demonstrated (1) an initial favorable response of objective symptoms, particularly those involving the joints, under treatment with cortisone in adequate dosage, as well as a clearing of facial erythema and a reduction in fever; (2) a relapse of symptoms in mild degree eight and 12 days, respectively, after each of the first two periods of administration; (3) control of symptoms for more than six weeks on a dosage of 100 mg. of cortisone on alternate days, not less; (4) suppression of the systemic reaction to complicating pneumococcus septicemia while the patient was under treatment with cortisone; (5) the development of signs of emotional imbalance on several occasions with sustained dosage of cortisone; (6) absence of fluid retention during cortisone therapy when dietary intake of salt was restricted, and (7) persistence of abnormal laboratory features of lupus erythematosus as well as a rise in serum globulin and an increase in urinary albumin.

COMMENT

Dosage.—ACTH was given to only one of the seven patients (case 3) in this series. It was administered for a period of 44 days in divided doses ranging from 10 to 80 mg. per day. At the end of the second week purulent peritonitis developed; multiple surgical procedures were necessary for the drainage of pocketed abscesses, and there was a stormy postoperative course. After a short interval in this case cortisone was administered for a period of 21 days. Signs of lupus erythematosus became subordinated to signs of secondary infection. The patient died a lingering death from inanition six months later. Since the effects of ACTH and of cortisone on the symptoms of lupus erythematosus in this case were comparable for purposes of discussion, the effects of these hormones will be considered in terms of cortisone.

Cortisone was administered in the form of cortisone acetate in aqueous suspension by means of intramuscular injection one or more times daily; in doses of 100 mg. per day or less, one injection seemed to be satisfactory. In one instance cortisone was administered continuously for a period of 166 days, for a total dose of 17.775 Gm. In the others, with the exception noted above, the administration was carried out in interrupted courses and the length of each course and the interval between courses varied with the symptomatic response of the patient or the development of untoward side effects. One patient had two courses of cortisone, with a total dose of 5.8 Gm.; three had three courses each, with a total dose of about 6.0 Gm., and 1 had four courses, with a total dose of more than 8 Gm. The usual plan of treatment was for an initial dose of 300 mg., then a dose of 200 mg. given daily for a few days until symptoms were controlled and then a daily dose of 100 mg. given for varying periods in order to test the maintenance level. Usually this dose sufficed to control symptoms. In a few instances a scheme of administration every other day was tried; doses of less than 100 mg. every second day invariably failed to suppress symptoms. After use of cortisone was discontinued, there was a lag of several days to several weeks before relapse occurred. In one instance (case 1) a moderate remission was maintained for more than 10 months after a long course of cortisone.

Symptomatic Response.—When the dosage of cortisone was adequate, the same familiar pattern of response was noted in each case, almost without exception, with

the first course of cortisone or with successive courses given in the face of relapse. Within two or three days the fever abated, stiffness and pain in the affected joints subsided and there was an improved sense of well-being with gain in appetite. In the second week, the facial erythema subsided, although in one instance (case 4), in which cutaneous signs were extensive and the skin was eroded, healing progressed slowly during each of several courses of cortisone with relapse occurring afterward. In most cases symptoms of malaise and a profound feeling of fatigue common to patients with lupus erythematosus were relieved within 10 days. Tachycardia and irregular pulse rates subsided; pleural and pericardial friction rubs disappeared, and effusions cleared, although a troublesome pleural pain persisted in one case as the main complaint. Several patients gained weight which was not accounted for by retention of fluid; during periods of remission, several of the bed-ridden patients were up and walking and even out of the hospital.

Unfortunately, these benefits for the most part were temporary. One patient (case 1) remained in a state of relative remission for more than 10 months after a protracted course of cortisone. A second (case 2) remained afebrile and free of symptoms of lupus erythematosus for more than two months after the first course of cortisone. The others had a return of some symptoms within seven to 21 days after cortisone was withdrawn, or sooner when the dose was gradually reduced before complete withdrawal.

Laboratory Response.—Results as seen by laboratory studies in this respect were disappointing. Anemia was improved occasionally during periods of well-being and of increased appetite during a course of cortisone, and leukopenia was less pronounced. Five of the seven patients had albuminuria of severe degree as a constant feature; this was not lessened by cortisone, and, indeed, occasionally it appeared to be aggravated. The serum albumin of the seven patients was consistently at low levels. Azotemia or increased blood pressure did not occur, except briefly in two instances. Serum globulin remained above the level of serum albumin, and this condition was not influenced by cortisone, except that in one instance the albumin-globulin ratio reached 1:1 and in another there was a reversal for a brief interval. The sedimentation rate of erythrocytes was unaffected by cortisone, for the most part; in no case did it return to normal even during the most encouraging periods of clinical remission.

A signal disappointment was the failure of cortisone to abolish the Hargraves phenomenon in the bone marrow, a sign which we have considered to be pathognomonic of the state of disseminated lupus erythematosus. Occasionally so-called L. E. cells were not clearcut, but always the specimens revealed signs of agglutination and the presence of amorphous material as indications of a positive reaction. The plasma test of Haserick was not applied in these cases. Finally, necropsy observations in the patients who died showed that the characteristic tissue reactions of disseminated lupus erythematosus had not been abolished.

Unfavorable Side Effects.—In general, cortisone in relatively large doses was well tolerated by patients with lupus erythematosus in the acute febrile phase of the disease. The pattern of unfavorable reactions to cortisone in rheumatoid arthritis has been discussed by Hench and his associates.[1a, b] In our cases of lupus erythematosus, in which renal damage was almost the rule, reactions appeared to be related

to the vagaries of the disease and variations in tolerance of the patient more than to the factor of the accumulation of the hormone under sustained dosage.

Retention of Salt and Water: Accumulation of interstitial fluid as a result of retention of salt during the administration of cortisone occurred in variable degree in six of the seven patients in this series, usually during the latter part of a course. This was minimal when dietary intake of salt was moderately restricted. However, in one instance (case 2), in the face of progressive renal damage, the accumulation of fluid during the second course of cortisone proceeded without restraint of diuretics to the point of pulmonary edema, hydrothorax, cardiac failure and death. In the milder cases diuresis of water and salt occurred within a few days after cortisone was withdrawn. Drop in the value for serum potassium to less than 3.0 milliequivalents per liter occurred in three cases, and in one there were significant electrocardiographic changes. These depressions occurred during periods of septicemia, major operative trauma or complete anorexia; they were temporary and were relieved by the administration of potassium chloride by mouth or by vein.

Nervous and Mental Symptoms: Nervous and mental symptoms occurred rather commonly in the patients with lupus erythematosus. Restlessness, irritability, shifting moods of depression and exaltation, insomnia, apprehensiveness, anxiety and phobias were seen; these usually were of mild degree. The usual euphoria associated with the administration of cortisone became exaggerated in one case to a state of insomnia, garrulousness, uncontrolled giggling and bulimia. In another, in which the record of the patient indicated prior emotional instability, there was a lighting up, under cortisone, of a severe anxiety neurosis with obsessions of guilt and compulsive trends to the extent that the patient was transferred to the psychiatric service at the hospital, where, after a period of weeks, there was a gradual return to normal. One patient had mild convulsions while receiving cortisone, and two patients had severe generalized convulsions during a critical phase of relapsing lupus erythematosus. Such complications are not unusual in cases of lupus erythematosus in which cortisone is not given.

Hypercortisonism: Rounding of the face occurred in two cases, but this was pronounced in only one (case 1), after prolonged administration of cortisone. Hirsutism, acne and striae to a mild degree occurred in two cases. These changes, except the striae, were reversible. There was no interference with the healing of wounds, abscesses, cutaneous ulcerations or eroded lesions of the skin by cortisone in the patients in this series.

Intercurrent Infections: Usual symptoms associated with septicemia, peritonitis, pneumonia and localized abscesses were almost entirely suppressed while the patients were under the effects of cortisone. In other respects, the hormone did not influence the usual course of the infection; the masking of symptoms may lead to a dangerous sense of false security and postponement of the use of necessary supplemental therapy.

Postcortisone Depression: When cortisone has been administered for long periods, symptoms of adrenal suppression may appear within a few days after withdrawal of the hormone. Such an effect, with weakness and a sense of depression, occurred in one instance (case 4) five days after the termination of a third course and lasted about one week. The adrenal glands of the patient (case 2) who died one week after the termination of a course of cortisone (2,000 mg. in 13 days) appeared

to be grossly atrophic. However, on microscopic examination, lipid granules were found in the zona fasciculata as an indication of functional activity. The detailed necropsy report on the third patient who died (case 6) is not completed.

Comparison with Observations.—As more liberal supplies of ACTH and cortisone became available during the past year, these hormones were applied to the study of lupus erythematosus in other clinical centers. In general, patients were selected who were critically ill, had a severe degree of renal involvement and often serous effusions and, occasionally, were moribund.[10] The published reports and personal communications are similar in most respects to what we have recorded here and what we observed originally in the case of the woman (case 1) to whom cortisone was given beginning in February 1949, namely, a striking initial symptomatic improvement, occasional remissions lasting from several weeks to several months but, in spite of all this, no significant influence on the characteristic laboratory phenomena or tissue reactions of the disease. Baehr and Soffer,[10b] in a discussion of their experiences with the administration of ACTH and cortisone to five patients with disseminated lupus erythematosus, mentioned a drop in serum globulin levels but no essential changes in the degree of leukopenia, the sedimentation rate or the L. E. cells observed in the bone marrow. Thorn and associates[10c] observed remissions of several months' duration after administration of ACTH to five of six patients, three of whom died subsequently. There was also a significant drop in the level of serum globulins while ACTH was being administered, and in one case L. E. cells could no longer be demonstrated. It has been our experience that the Hargraves phenomenon is reduced in intensity but never abolished; evidences of clumping of cells and the presence of amorphous material persist even though the characteristic cell structure can no longer be demonstrated.

The effectiveness of these hormones in producing remissions in the acute phase of lupus erythematosus is noteworthy; however, it is well known that remissions and relapses form a familiar sequence in the natural course of the disease, even in its fulminating phases. Baehr and Soffer emphasized the critical nature of the side effects of these hormones, particularly disturbances in electrolytes which, in patients with severe renal impairment, may lead to uncontrollable fluid imbalance. They maintained, wisely, that use of these hormones should be confined to conditions which can be adequately controlled at all times.

SUMMARY AND CONCLUSIONS

Our experience with the administration of cortisone and ACTH to seven women who had the acute phase of lupus erythematosus indicates that these hormones exert a striking effect on the presenting symptoms of the disease, improve the well-being of the patient and promote remissions in some cases. They bolster the patient against stress and crises, ordinarily disastrous in this disease. Wound healing is unimpaired. These benefits are temporary; there has been no significant improvement in the characteristic laboratory phenomena or the tissue reactions of the disease. Side effects produced by these hormones in cases of lupus erythematosus, in which severe

10. (*a*) Footnote 4. (*b*) Baehr, G., and Soffer, L. J.: Treatment of Disseminated Lupus Erythematosus with Cortisone and Adrenocorticotropin, Bull. New York Acad. Med. **26**: 229-234 (April) 1950. (*c*) Thorn, G. W.; Forsham, P. H.; Frawley, T. F.; Hill, S. R., Jr.; Roche, M.; Staehelin, D., and Wilson, D. L.: The Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**:825-834 (May 25) and 865-872 (June 1) 1950.

renal impairment is the rule, are considerable. Disturbances of behavior, even psychotic episodes, may occur, but these are reversible. Caution must be maintained in the administration of these hormones. They should be given only when laboratory facilities are available for strict control of the conditions. Their chief field of usefulness in lupus erythematosus will be in the management of cases in which irreversible systemic damage has not occurred. This field is being explored now.

ABSTRACT OF DISCUSSION

ON PAPERS BY DRS. TRAUB AND SPOOR AND BY DRS. BRUNSTING, SLOCUM AND DIDCOCT

DR. PAUL A. O'LEARY, Rochester, Minn.: Observations on the physiological effects of cortisone and on those of ACTH in man are very similar, as reported by Sprague and his collaborators. The physiological changes these authors observed included a number of cutaneous lesions; in addition they recorded many laboratory data, and no doubt the studies now going on will reveal subsequently other important observations. The features of Cushing's syndrome were induced frequently after administration of large doses of cortisone for a long time.

The "squirrel face," the result of facial edema, with change in the facial contour, hirsutism, acne, keratosis pilaris, cutaneous striae, edema and muscular weakness appeared in various combinations in the patients treated and irrespective of the disease for which this treatment was given. In addition to these cutaneous changes, amenorrhea and mental depressions were noted. The impairment of carbohydrate tolerance, negative nitrogen balance and increased excretion of corticosteroid in the urine (and hypochloremic hypopotassemic alkalosis) were noted in varying degrees and amounts in various patients. My associates and I have also noted, as Dr. Traub reported, that creatinine and uric acid excretions were increased in the urine. Likewise, the hematological changes were not significant, as most patients showed a slight increase while others showed a decrease in the number of white blood cells.

The function of the adrenal cortices was depressed or put at rest temporarily. In addition to other inconstant physiological changes, which seem irrelevant to this discussion, it is important to note that cortisone may produce death, which may be sudden and unanticipated and not always explained by the observations at autopsy.

A survey of these physiological functions would seem to indicate that the so-called "collagenous diseases" would not be benefited materially by either cortisone or ACTH; nevertheless, a therapeutic trial of these agents seemed warranted in these diseases, for which we have so little to offer from the treatment standpoint; in contrast to Dr. Traub I agree with Montgomery and McCreight, who believe that the collagen or fibrinoid degeneration in the walls of the vessels of the skin in lupus erythematosus is so minor that the inclusion of this syndrome in the group of the so-called collagenous diseases is not justified. Less than one fourth of the 192 cases of all types of lupus erythematosus examined by them showed any significant alterations in collagen, certainly not more than may be noted in other inflammatory skin diseases.

As Dr. Brunsting pointed out, the clinical improvements the patients with lupus erythematosus displayed were in the main of a temporary and symptomatic type and not of a fundamental or basic nature. It is especially significant that in those who died the autopsy showed the unaltered characteristic pathological processes; likewise the laboratory data characteristic of lupus erythematosus were unchanged, and the L. E. cells, although found less frequently after treatment, were still present in spite of the symptomatic improvement noted by these patients.

Four patients with acrosclerosis—or, if you prefer, Raynaud's disease with scleroderma—were also treated with cortisone. The improvement they displayed has been more pronounced than that noted in the patients with disseminated lupus erythematosus. The improvement was evidenced by a definite decrease in the cutaneous sclerosis, especially of the hands, loss of joint pains and stiffness and gain in weight (not edema). Most of the improvement occurred after the second course of treatment. However, of special significance was an increase of from 3 to 5 degrees F. observed in the temperature studies of the fingers. The increase in

the heat output of the fingers, indicative of an increase in the blood flow, follows the injection of 100 mg. of cortisone and remains for several hours. Unfortunately, the softening of the skin begins to disappear, with recurrence of the sclerosis, several weeks or longer after discontinuance of the cortisone therapy. One patient, who had had 1,200 mg. of cortisone in January 1950, returned in May because the cutaneous sclerosis had begun to recur. A second course of cortisone, at the rate of 100 mg. per day, was started. After four days of treatment the patient became ill with fever, acquired a morbilliform eruption and died within 48 hours in convulsion. Autopsy of the head was not permitted.

We have also treated three patients with dermatomyositis, one each of the acute, subacute and chronic types. The condition in the fulminating febrile phase was unimproved, although some gain in muscle strength was noted in the chronic phase, but no fundamental alteration for the better could be recognized in the tissues.

Patients with the following types of bullous diseases have also been given cortisone: pemphigus vulgaris, one case; pemphigus foliaceus, three cases, and severe erythema multiforme, one case. These blistering eruptions responded temporarily, as was evidenced by recession of the bullae while the condition was under the influence of cortisone. Also there was improvement in the sense of well-being and healing of the erosions of the skin. In one early case of pemphigus foliaceus the lesions completely involuted and remained so for three months. In another patient with pemphigus foliaceus there was temporary improvement twice, each time following a course of cortisone, but during the week of postcortisone depression there was an aggravated recurrence of blistering and dissolution of the skin.

The four patients with psoriasis and psoriatic arthritis showed prompt response to cortisone therapy, especially in the articular symptoms, the skin responding more slowly. However, when the cortisone therapy was stopped there was return of the cutaneous and joint symptoms. In one of these patients there was a pronounced aggravation of a previous mild psychotic state.

These observations of a comparatively few cases indicate what may be the therapeutic limitations of cortisone and ACTH in the treatment of patients with these types of cutaneous disease. Further trial of the remedies in early cases, before irreparable damage has been done, may warrant a more optimistic viewpoint.

DR. UDO J. WILE, Ann Arbor, Mich.: These papers on disseminated erythematous lupus have been of great interest to all of us, particularly in view of the successful and occasionally disappointing results in the treatment of disseminated lupus erythematosus with both ACTH and cortisone. I am suggesting that the time has now come for us to differentiate, in writing and in discussion, disseminated discoid lupus erythematosus and the more serious cases. When visceral manifestations, with blood dyscrasias, arthritis, septic temperature and occasional polyserositis are present, the designation systemic erythematous lupus would better be used.

The incidence of this last group has increased amazingly during the past 15 or 20 years. I believe this increase is real rather than apparent. At the University Hospital the number of cases of all types of lupus erythematosus during the last 15 years has increased 100 per cent; however, the number of cases of systemic lupus erythematosus in this group shows an increase during this period of 450 per cent. Is there not an inference in this fact that there is something which people are now doing or certain circumstances which coincide in time with this increase that may be responsible factors? In this connection it is interesting to recall that in the previous 15 years there was an enormous increase in the incidence of agranulocytic angina. It soon became evident that this previously rare condition was precipitated by the general use of drugs of the antipyrine and aminopyrine series. A certain number of cases were directly due to Salvarin derivatives. Patients who died from this condition presented much the same picture, both clinically and pathologically, as those whom we now see dying of systemic lupus erythematosus. In both instances the picture resembled a sepsis; in both there was high temperature, pronounced disturbance of hematopoiesis and secondary anemia. Coincident in time with the increased incidence of systemic lupus erythematosus there came into the picture the more or less general use of the sulfonamide drugs, first used for serious infections such as pneumonia. It soon became a general habit for many people to use sulfonamides for common colds and for all types of infections. A large majority of

patients with systemic lupus erythematosus are shown to be photosensitive, and it might properly be recalled that the barbiturates and their forerunners and the sulfonamide drugs have experimentally been shown to be photosensitizing agents.

Many of our patients date the onset of their first symptoms to sunburn or exposure to ultraviolet or roentgen radiation. Is it not a suggestive hypothesis that photosensitivity, either inherent, as in redheaded or blond persons, or induced by photosensitivity-producing drugs, may constitute a trigger mechanism leading to the severe allergic reactions in the viscera and the blood-forming organs and to the other manifestations so characteristic of this disease?

DR. CHARLES C. DENNIE, Kansas City, Mo.: Also, one must take into account—I have had the same idea as Dr. Wile—that during the years 1934, 1935 and 1936 there were terrible droughts all over the Midwest, with extremely high temperatures and practically no clouds —sunlight for over 90 days without a cloud.

DR. WILLIAM H. GOECKERMAN, Los Angeles: I have had no personal experience with the use of cortisone and very little with that of ACTH, but I have been interested in hormone therapy for many years and have followed the literature rather critically not only so far as it pertained to clinical work but also with regard to animal experimentation and the work of biochemists and physiologists and so forth. As a result of this intense interest in hormone therapy I have some thoughts which I think might be of some interest.

It is very fascinating to see the intensive biochemical study which the discovery of ACTH and cortisone has brought about. As yet I cannot see that these studies have much clinical significance. My hope is that eventually out of these studies may come a laboratory test or tests which may guide us in hormone therapy. Urologists began to treat carcinoma of the prostate with estrogens about 10 years ago. The first reports emphasized a high percentage of symptomatic response; however, after a year or two there was a relapse and then, no matter how high the dose, estrogens were no longer of value.

Now reports of six, eight and even nine years of symptomatic responses are reported. There was even about a year ago a report from Johns Hopkins of a patient whose carcinoma had been diagnosed by microscopic examination, who had died from an intercurrent disease, in whom at necropsy the prostate was observed to be normal. Yet, after all these years the urologist is chiefly dependent on clinical judgment. It must be evident, however, that he has learned to use the hormones with better judgment. My own interest in the treatment of acne vulgaris with hormones now is of about 15 years' duration, more specifically for the last 10 years. There has not been suggested a laboratory guide in administering the estrogens that I could find. According to my experience, if one is satisfied with—let us say—response in 30 to 40 per cent of the patients, then maybe routine administration is perfectly adequate. But if one wishes to achieve a satisfactory result in 90 or 95 or even 98 per cent it eventually becomes a matter of nicety of judgment whether to increase or decrease the dose in a given patient. There usually comes a time during the use of estrogens in acne when the eruption gets worse during the routine administration; then to judge just what move to make without any guidance from the laboratory is sometimes very difficult, and only experience gradually decides the move.

It may be said that probably the group interested in the treatment of Addison's disease has done the best work so far to evaluate laboratory tests. With the advent of ACTH and cortisone—far more powerful hormones than any we have had before—such a guiding test seems more important than ever. To justify my longing for such a test I should like to propose a concept, if not a theory or possibly even a fact. If one judges by the writings of some of the men who do experimental work in animals, this concept possesses rather largely what they feel is already established as truth. I am not sure about that. This concept has considerable clinical support but much more encouragement as a result of animal experimentation. It assumes that all steroid hormone therapy is indirect and exerts its effect on certain target organs of a given individual. These target organs are probably the so-called endocrines, and also the pancreas and liver, but which ones they are in a given instance naturally varies with the hormone therapeutically employed. These organs vary decidedly in their efficiency and response in different individuals. The targets are certainly not the adrenal glands alone. I think that individualization of the patient is far more important

with hormone therapy than with any other form of treatment at our command. This point was constantly exemplified in my work with acne vulgaris. Since hormone therapy must usually be continued over a considerable period, the target organs may be temporarily overstimulated or exhausted. If the dose is too small there will be no clinical response. This concept will also readily explain the shockingly good symptomatic results obtained in diseases of variable character and type.

In view of the recent employment of cortisone and ACTH in a great variety of diseases, with results which have been very striking and brilliant but temporary, the thought arises of whether or not the patients should be more critically individualized. Possibly, instead of giving the minimal therapeutic doses as ordinarily accepted, one might make the dose so small as to remind one of the days of homeopathy.

If this concept is correct, one can readily understand that no permanent result might be obtained in advanced cases of arthritis or acute lupus erythematosus because the target system may be exhausted and the therapeutic effect is merely a whipping-up of tired organs. The essence of this discussion implies that there is much room for technical improvement in the use of all steroid hormones. With the advent of proper laboratory tests, the therapeutic technics would probably receive a considerable impetus for the better. I am quite optimistic as to results, not so much in the very severe diseases but in some of the lesser problems. If we keep in mind this particular theoretical approach, our results will probably excel those we have obtained in the past.

DR. FRANK C. COMBES, New York: While I was listening to these interesting discussions the thought came to me that there are none of the usual signs or symptoms of adrenal insufficiency in subacute lupus erythematosus. Furthermore, it is interesting that the salicylates and adrenocortical hormones are similar in their effects: namely, they both lower fever; both to some degree reduce the sedimentation rate; both increase the neutrophils; both cause hyperglycemia, and, finally, both are effective in therapy of subacute lupus erythematosus and arthritis.

Still another feature interested me. Isn't it odd that there is a negative nitrogen balance in scleroderma and acrosclerosis when both diseases are helped by cortisone, which of itself is productive of a negative nitrogen balance? One would expect cortisone to cause aggravation of the sclerosis. Dr. Co Tui and I have been able to effect material improvement in scleroderma by putting the patient on a high protein diet.

DR. HARRY L. ARNOLD, JR., Honolulu, T. H.: I should like to mention a singular case, which bears on both of these papers and on much of the discussion that has been made, of a patient with characteristic chronic disseminated lupus erythematosus whom I have observed over a period of six years. During this time she has never at any time shown more than an occasional trace of albumin in the urine, but the other observations are all characteristic, including the demonstration of the L. E. factor in her plasma by Dr. Haserick.

She has been seriously ill from time to time and moderately ill all the time for this six year period of observation. Her plasma cholesterol when she was first seen by us was 30 mg. per 100 cc., and it remained at that level for some weeks, while my associates and I temporized, not being sure of the diagnosis; then we made up our mind that she did have disseminated lupus erythematosus and gave her iodine, intermittently because she did not tolerate it well. Her condition improved generally fairly steadily, and her cholesterol level rose steadily.

She became intolerant of the iodine, and its use was stopped; in a period of a month or two she went into relapse and the cholesterol level went down to 40 mg. per 100 cc. We gave her crude liver extract intramuscularly, and again the cholesterol level climbed; she then broke treatment because she felt so well, remained away for six or eight months and came back and reported that she had had fever often but had been able to do her housework but that she was now too ill to do it. Dr. Harold Johnson then gave her a bismuth preparation intramuscularly. She responded dramatically to this treatment and again her cholesterol level climbed, this time to 120 mg. per 100 cc. over a period of three or four months. Her condition again improved. At the time this result was completely mysterious to us, but it seems quite probable now in view of the recent demonstration that esterified cholesterol is essential to the

synthesis of adrenal steroid hormones. Perhaps this provides one explanation of the otherwise mysterious common denominator among those three methods of treatment—iodine, bismuth and crude liver extract.

I should like to point out, in reference to Dr. Combes' statement that these patients do not show signs of adrenal deficiency, that most of them do show one cardinal sign, namely, a sense of weakness. This was reported by Dr. Montgomery a couple of years ago as being present in all the cases of lupus erythematosus in his series, and certainly it is a characteristic observation in adrenal insufficiency.

DR. STEPHEN ROTHMAN, Chicago: I should like to ask Dr. Brunsting whether he noted that in acne following the administration of ACTH or cortisone there is no obvious seborrhea. In our cases it seemed that ACTH is responsible for follicular hyperkeratosis rather than for hyperplasia of sebaceous glands. There was no seborrhea—only comedos, papules and pustules. The pubertal development of sebaceous glands is still not well understood. Male sex hormones are powerful growth stimuli, but the incidence of acne is about equal in the two sexes. If we assume that adrenocortical hormones are responsible for the pubertal development, it remains unexplained why male castrates do not ever display acne.

DR. EUGENE F. TRAUB, New York: The reasons for using the preparation employed in our cases were its availability and the fact that it seemed to give less reaction than some of the other new preparations of the same general type. For this last reason we felt that if the treatment proved successful a maintenance dose might possibly be arrived at which might not prove toxic to the patient over a longer period. It is possible that if we had had more acute cases the results might have been more striking. Certainly for the chronic discoid cases, even when they showed some dissemination, the results were disappointing.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: We have observed a masking of symptoms on several occasions in our experience with patients with disseminated lupus erythematosus—septicemia in one case, peritonitis in a second and terminal hemorrhagic pancreatitis in a third—in all these intercurrent insults the systemic reactions being almost completely suppressed by the action of the hormone.

The increase in the recorded incidence of disseminated lupus erythematosus may be accounted for to some extent by the education of the general practitioner in regard to the protean manifestation of the disease in the early phases, as well as by the general increase in the use of hospital facilities for sick patients in recent years and the application of the Hargraves test to borderline cases, especially those in which cutaneous signs are absent or atypical. The factors of sun and other items to which these patients are sensitive should be regarded as a phase of the general reactivity of the disease rather than as fundamental to the etiology. During the use of cortisone and ACTH in long and continued dosage, occasionally signs of keratosis pilaris as well as acneform comedos and pustules appeared on the skin, but the seborrheic pattern usually associated with acne vulgaris was lacking.

MORPHEA-LIKE EPITHELIOMA

MARCUS R. CARO, M.D.
Clinical Professor of Dermatology, University of Illinois College of Medicine
CHICAGO
and
J. B. HOWELL, M.D.
Instructor in Dermatology, Southwestern Medical College, University of Texas
DALLAS, TEXAS

IN RECENT years there has been evident a growing tendency to shrink the domain of dermatology by removing from it diseases in which dermatologists have done pioneer work but in which others are now showing an acute interest. Great technical advances in special forms of treatment, to which dermatologists have themselves made important contributions, have tended to divert patients from the care of dermatologists and to channel them to specialists in those modalities. This trend has been particularly great in the field of cutaneous cancer.

Dermatologists are by teaching and experience trained to reach a correct diagnosis early in the presence of an epithelioma. Because of their knowledge of the clinical course and histopathological differentiation of the various types of epithelioma they are also well qualified to render an impartial decision as to the kind of treatment most suitable for any individual lesion. Therapeutic specialists, whether radiologists or surgeons, may tend in each case to resort to the one treatment in which they are most proficient. A nondermatologist may also at times be led astray by a histopathological report which a dermatologist would observe to be inconsistent with the clinical features of a case.

These remarks apply particularly to lesions that have been designated as morphea-like epithelioma, scleroderma-like epithelioma and scirrhous epithelioma. To the inexperienced observer the lesion appears to be morphea more often than it suggests cancer. In addition, for complete eradication it generally calls for skilled individualization of treatment rather than the routine management that is often assigned to cancer.

CASES PREVIOUSLY REPORTED

The first case of morphea-like epithelioma was presented by Crocker [1] before the International Congress of Dermatology in London in 1896, but it was not diagnosed at that time. The same case was later reported by Pernet [2] in 1912 as morpheiform rodent ulcer.

Read at the Seventieth Annual Meeting of the American Dermatological Association, Inc., Jasper National Park, Alberta, Canada, June 21, 1950.

1. Crocker, H. R., in Official Transactions, Third International Congress of Dermatology, London, Aug. 4-8, 1896, London, 1898.

2. Pernet, G.: Morpheiform Rodent Ulcer, Ikonograph. Dermat. **6**:243, 1912.

The first actual report of this tumor was by Danlos,[3] who in 1899 presented the case of a man with a round plaque, 6 cm. in diameter, on the nape of the neck. There was a ringlike border about 1.5 cm. broad, of a yellowish hue, traversed by numerous vessels which ran from the periphery to the center of the plaque. About this slightly elevated ring was a lilac-colored zone, while the central portion showed an irregular ulcerated surface. Biopsy showed epithelioma, and the case was presented as an epithelioma simulating morphea or xanthoma. In his discussion Brocq stated that he had seen two similar cases.

At the meeting of the American Dermatological Association in 1899 Stelwagon [4] presented the case of a man aged 40 who had a flat epithelioma of the temporal region with a superficial 1 inch (2.5 cm.) wide border resembling morphea.

In a paper discussing unusual forms of epithelial growths Fordyce [5] in 1908 described as a trichoepithelioma a round sclerous papule, 3/8 inch (1 cm.) in diameter, occurring on the lip in a man aged 80. The description of the lesion and the photomicrograph are diagnostic of morphea-like epithelioma.

Hartzell [6] in 1909 presented four more cases of this disease, and in the following discussion Fordyce, Hazen and Pusey cited similar cases of their own.

Heidingsfeld [7] in 1913 reviewed the cases previously reported, and he described a quarter-dollar-sized morphea-like patch occurring on the cheek of a man aged 38. The diagnosis of morphea-like epithelioma was confirmed by biopsy, and the lesion was treated with roentgen rays in 1911. The patient was seen again in 1915, when the morphea-like appearance was lost and the well defined malignant character of the lesion was definitely established. The cancer again improved after treatment with radium, but it was not completely destroyed at the time of the subsequent report.[8]

Additional cases of morphea-like epithelioma have been reported by Levin,[9] Michelson,[10] Montgomery and Culver,[11] Traub,[12] Gougerot and Eliascheff,[13]

3. Danlos, M.: Morphea-like Epithelioma, Ann. de dermat. et syph. **10**:656, 1899.

4. Stelwagon, H. W.: Morphea-like Epithelioma, in Transactions of the American Dermatological Association, 1899, p. 166.

5. Fordyce, J. A.: Some of the More Unusual Forms of Epithelial Growths of the Skin, J. A. M. A. **51**:1398 (Oct. 24) 1908.

6. Hartzell, M. B.: Morphea-like Epithelioma, J. A. M. A. **53**:262 (July 24) 1909.

7. Heidingsfeld, M. L.: Morphea-like Epithelioma, J. Cutan. Dis. **31**:379, 1913.

8. Heidingsfeld, M. L.: Morphea-like Epithelioma Treated with Radium, J. Cutan. Dis. **36**:313, 1918.

9. Levin: Morphea-like Epithelioma, J. Cutan. Dis. **37**:488, 1919.

10. Michelson, H. E.: Basal-Cell Epithelioma of the Morphea Type, Arch. Dermat. & Syph. **7**:848 (June) 1923; ibid. **16**:790 (Dec.) 1927.

11. Montgomery, D. W., and Culver, G. D.: Scleroderma-like Epithelioma, Arch. Dermat. & Syph. **18**:281 (Aug.) 1928.

12. Traub, E. F.: Morphea-like Basal-Cell Epithelioma, Arch. Dermat. & Syph. **22**:1118 (Dec.) 1930.

13. Gougerot, M. H., and Eliascheff, O.: Sclerodermiform Basal Cell Epithelioma, Bull. Soc. franç. de dermat. et syph. **42**:1785, 1935.

Vilanova,[14] Abramowitz,[15] Goodman,[16] Esteller and Errando,[17] Vilanova and Calap,[18] Johnson,[19] Costello,[20] Madden,[21] Finnerud [22] and Torrey.[23]

The comparatively small number of cases reported may suggest that morphea-like epithelioma is a rare disease. It is our feeling, however, that cases of this form of cancer are diagnosed and treated much more frequently than a perusal of the literature would indicate.

CLINICAL FEATURES

During the past 20 years an examination of 11,779 cutaneous biopsy specimens resulted in the diagnosis of malignant epithelial tumor for 2,116. Of these cancers 34 were acceptable as being morphea-like epithelioma on both clinical and histopathological grounds, and they occurred in 33 patients, one patient having two independent lesions.

Twenty-one patients were women and 12 were men. Their ages varied from 35 to 78 years. The duration of the lesions was stated to be from four months to 20 years, but these figures cannot be exact, for lesions of this type may for a long time be unobtrusive.

In 31 of the patients the lesions were located on the face, while in two they were on the neck, below the ear. Of the facial lesions 14 were on the cheek, eight on the forehead or temple, five on the nose, four on the chin, and one on the left upper eyelid.

The lesions varied from 0.5 cm. in diameter for young lesions to 7 by 8 cm. for a patch on the forehead in one patient (fig. 1), in whom the lesion had been present for about eight years and had recurred once after roentgen ray treatment and again after therapy with the Sherwell technic and electrodesiccation. In most cases the epithelioma was round or oval. Occasionally, however, the direction of growth produced elongated patches, as in one patient (fig. 2), in whom a lesion had been treated by the Sherwell technic and radium 10 years ago, which therapy had been followed by a recurrence at both the upper and the lower pole of the resulting scar.

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14. Vilanova, X.: Scirrhous Form of Epithelioma Simulating Scleroderma, Actas dermo-sif. **27**:416, 1935.

15. Abramowitz, E. W.: Morphea-like Type of Basal Cell Epithelioma, Arch. Dermat. & Syph., **37**:910 (May) 1938.

16. Goodman, H.: Morphea-like Epithelioma of Nasolabial Fold, Arch. Dermat. & Syph. **40**:1051 and 1061 (Dec.) 1939.

17. Esteller, J., and Errando, E.: Sclerodermiform Epithelioma, Actas dermo-sif. **36**:1017, 1945.

18. Vilanova, X., and Calap, J.: New Case of Epithelioma with Aspect of Scleroderma, Actas dermo-sif. **37**:244, 1945.

19. Johnson, H. W.: Morphea-like Basal Cell Epithelioma with Ulceration, Arch. Dermat. & Syph. **53**:52 (Jan.) 1946.

20. Costello, M. J.: Morphea-like Epithelioma and Basal Cell Epithelioma of the Face Cured by Roentgen Ray Therapy, Arch Dermat. & Syph. **55**:585 (April) 1947.

21. Madden, J. F.: Basal Cell Epithelioma, Morphea Type, Arch. Dermat. & Syph. **56**:131 (July) 1947.

22. Finnerud, C. W.: Case for Diagnosis (Morphea Type of Epithelioma), Arch. Dermat. & Syph. **57**:429 (March) 1948.

23. Torrey, F. A.: Basal Cell Epithelioma, Morphea-Like Sclerosing Type in the Nasolabial Fold, Arch. Dermat. & Syph. **60**:1053 (Nov.) 1949.

The type of lesion seen most frequently was a slightly elevated papule or patch with a well defined border that could be palpated better than seen (fig. 3). Small papules were flat topped, but in larger lesions the center was depressed and

Fig. 1.—Ulcerated and invasive lesion on the forehead, 7 by 8 cm., of eight years' duration. There was recurrence after roentgen ray treatment three years before and again after use of the Sherwell technic and electrodesiccation one year before.

Fig. 2.—Bandlike recurrence on the left side of the neck both above and below the scar resulting from treatment with the Sherwell technic and radium 10 years before.

saucer-like. The consistency was very firm, and the lesion gave the impression of a disk inserted into the skin. The color was grayish or yellowish white; the surface was generally smooth and shiny, and telangiectasias were seen in most cases. In several cases ulceration was present, but this occurred in older and

larger lesions. Occasionally an adherent scale covered the depressed center of a lesion even in the absence of ulceration.

The growth of the tumors was very slow, and most of the lesions were superficial. In only two cases, one of eight years' duration on the forehead (fig. 1) and one of three years' duration on the temple, were there deeper invasion and attachment to underlying muscle or bone. In the latter case the increased activity of the malignant cells was suggested also by the appearance of a small elevated nodule arising from the lower border of the tumor. In no instance was there any evidence of metastasis or involvement of the regional lymph nodes.

Fig. 3.—Saucer-like lesion on the chin, 2 by 1.25 cm., of five years' duration.

HISTOPATHOLOGICAL FEATURES

Of the 34 specimens examined 32 were basal cell epitheliomas while two were of the prickle cell variety.

One of the prickle cell lesions occurred on the left cheek of a woman 35 years of age who had received many roentgen ray treatments to the face several years before the appearance of the epithelioma. In the histological section (fig. 4) the malignant cells were arranged in elongated and anastomosing strands of pale-staining cells which in several places had produced small horn pearls. Several of these cornified nests had undergone calcification. The other prickle cell epithelioma (fig. 3) was on the chin of a man aged 62, who had the weather-beaten skin of a farmer. In this patient a basal cell morphea-like epithelioma of the left upper eyelid had been treated successfully with interstitial low intensity radium needles three years previously. In the section from the chin lesion (fig. 6) the upper

part of the corium was filled by many interlacing strands of pale-staining cells separated by a small amount of densely packed fibrous connective tissue. A few granules of calcium were present. The superficial blood vessels were dilated.

In several of the specimens of the basal cell variety there were seen occasional keratinous cysts just beneath the epidermis which might on casual examination be mistaken for the horn pearls of prickle cell epithelioma. These cysts, however, showed an abrupt demarcation between the epithelial lining and the keratinous

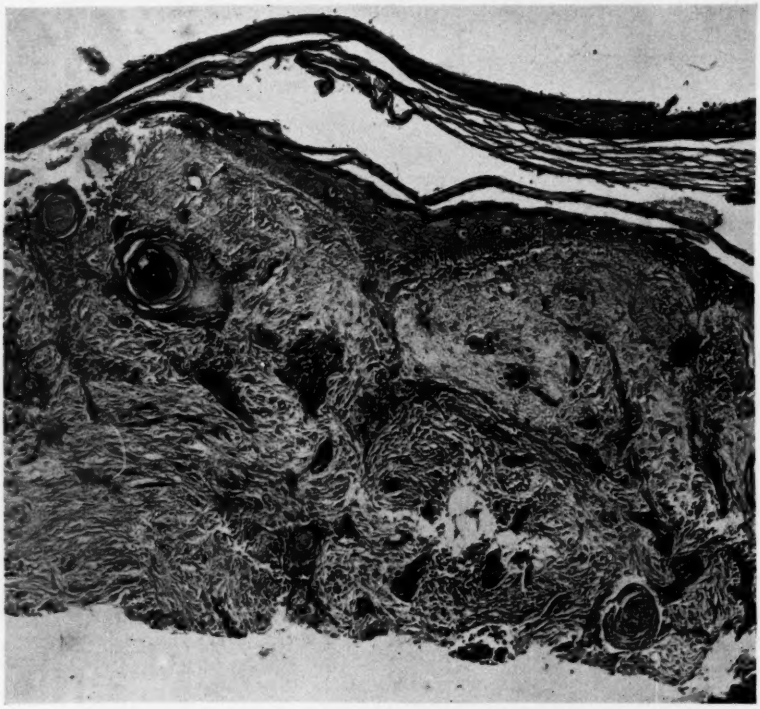

Fig. 4.—Prickle cell morphea-like epithelioma showing horn pearls and calcification of some of the keratinous nests; hematoxylin and eosin stain, × 100.

center, and they probably represented cross sections of invaginations from the surface.

In all sections from the basal cell lesions the individual cells were elongated, dark-staining and densely packed, having the appearance of cells seen generally in basal cell cancer. The distinguishing feature of morphea-like epithelioma was the grouping of these cells into elongated strands, some showing several cells packed closely together and others attenuated to a thickness of one cell. For the most part these strands were short and isolated (fig. 7), but in some lesions they were long and anastomosed in all directions to produce a bizarre network. Separating

these groups of malignant cells was a densely packed connective tissue which contained both collagen and elastic fibers.

In early lesions the tumor mass lay as a narrow horizontal band high in the corium and there was a sharp line of demarcation separating the tumor from the normal surrounding tissue (fig. 8). In older lesions the malignant cells became more invasive and the tumor mass was disorganized by lateral and downward extensions of both the strands and the individual cells (fig. 9). In sections of several of these invasive lesions there were numerous mitotic figures.

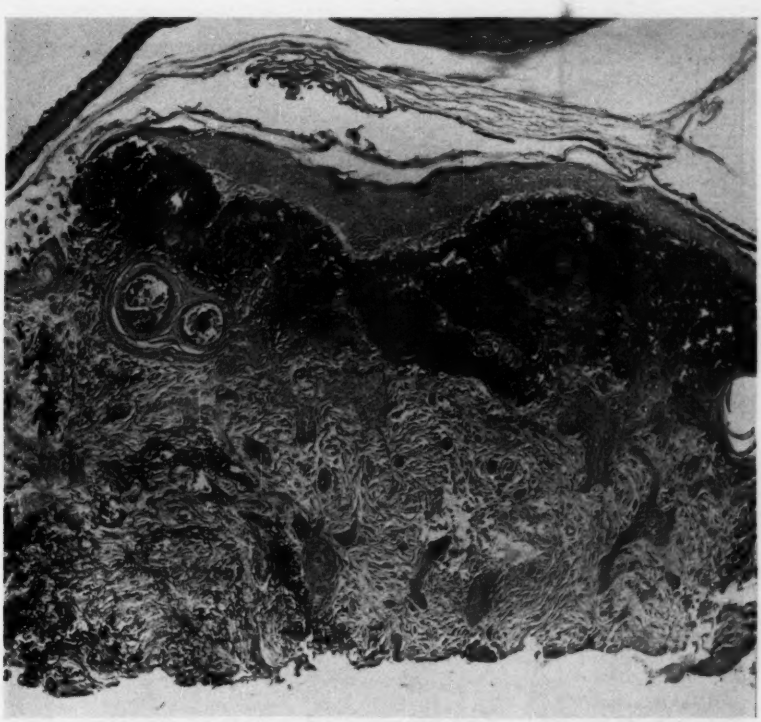

Fig. 5.—Subepidermal band of senile elastosis shown in the same specimen illustrated in figure 4; Weigert stain, × 100.

In only two sections could a connection be demonstrated between the tumor cells and the basal layer of the epidermis. In all the others there was an intervening layer of corium in which the blood vessels were appreciably dilated. In most of the sections there was no evidence of inflammatory reaction, but in those taken from ulcerated lesions the stroma contained a dense infiltrate of lymphocytes, plasma cells and polymorphonuclear leukocytes.

Hair follicles were demonstrable in several cases. In most of the sections, however, hairs, sebaceous glands and sweat glands were absent in the area invaded by the cancer and could be seen only in the tissue surrounding the tumor mass.

In all the sections there were varying amounts of pale-staining homogeneous material lying just beneath the epidermis and in several instances extending downward to lie between the groups of tumor cells. Staining with the Weigert stain (fig. 5) demonstrated that these masses were composed of thick and fragmented elastic fibers interspersed with a homogeneous aggregation of degenerated elastic fibers designated as senile elastosis.[24] Staining with the Van Gieson stain showed that even within these degenerated areas some of the collagen fibers were distinct and well stained. Sections stained with sudan III did not show the presence

Fig. 6.—Prickle cell morphea-like epithelioma, a section from the lesion on the chin illustrated in figure 3; hematoxylin and eosin, × 180.

of lipids in the areas of senile elastosis or in the tumor. Sections stained with the von Kossa stain failed to demonstrate any calcification of the areas of senile elastosis, the tumor cells or the dense fibrous stroma. With this stain, however, it was possible to demonstrate more clearly the granules of calcium lying freely in the tissues and also the transformation of some of the keratinous cysts into tiny calcareous nodules.

24. Weidman, F.: The Pathology of the Yellowing Dermatoses: Nonxanthomatous (Jaundice, Carotinemia, Blood Pigmentation, Melanin, Colloid Degeneration and Elastic Degeneration), Arch. Dermat. & Syph. **24**:954 (Dec.) 1931.

The morphea-like appearance of the lesion is undoubtedly produced by the dense packing of fibrous stroma about the strangled nests of cancer cells. The patterning of the tumor as a flat horizontal subepidermal band does not tend to produce the raised nodular border that is seen in other types of cutaneous cancer. The senile elastosis present in these lesions may be a contributing factor to the sclerotic nature of the papule. If so, however, it is a minor factor, for the firmness of the lesion is not proportional to the varying degrees of senile elastosis present in different cases.

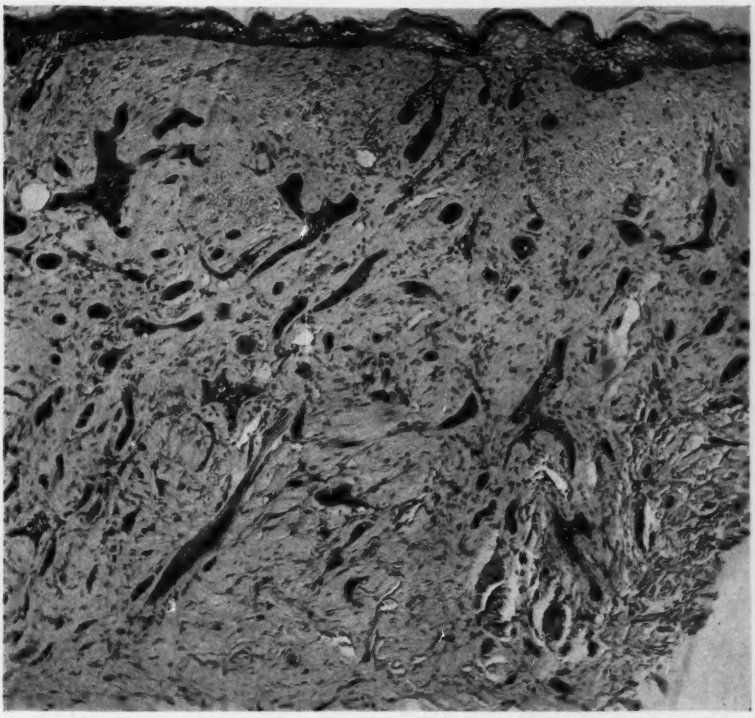

Fig. 7.—Basal cell morphea-like epithelioma, a section from the lesion on the forehead illustrated in figure 1; hematoxylin and eosin, × 100.

DIFFERENTIAL DIAGNOSIS

Morphea-like epithelioma may at times be confused with lesions of other dermatoses that are chronic, well circumscribed and sclerotic.

Morphea is always simulated. Morphea-like epithelioma is distinguishable by its almost invariable location on the face or neck, the insidious onset as a small papule followed by a very gradual peripheral enlargement, the telangiectatic vessels seen on the surface and, in some cases, eventual ulceration. These features are generally lacking in morphea.

Senile elastosis in most instances is a diffuse yellowing degenerative change in the skin seen on the face and neck of persons who have long been exposed to the aging process of the sun and the years. We have seen several patients, however, in whom these degenerative changes occurred in the form of well circumscribed firm papules or patches which were mistaken grossly for epithelioma. Because these lesions of localized senile elastosis occur principally on the face, a clinical differentiation from morphea-like epithelioma is not always possible. The absence

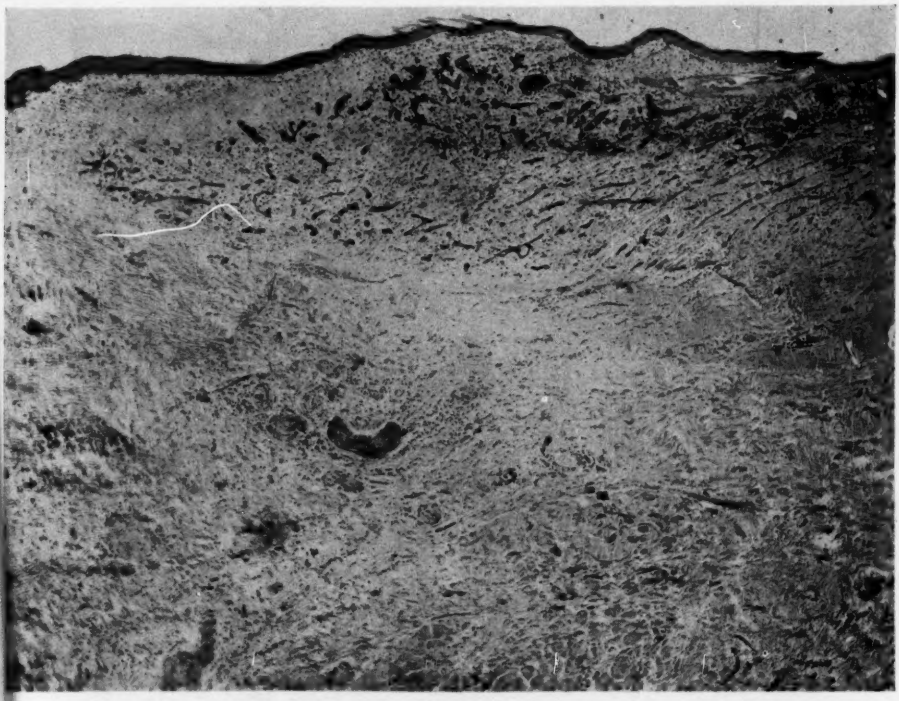

Fig. 8.—Basal cell morphea-like epithelioma, section demonstrating the superficial location of the circumscribed horizontal band of cancer cells; hematoxylin and eosin, × 43. (Courtesy of Dr. Udo J. Wile.)

of telangiectasia and ulceration in these lesions would aid in ruling out the presence of cancer, but only a biopsy can make the differentiation certain.

Lupus erythematosus lesions in most instances can be diagnosed on the basis of the characteristic scale and the keratotic plugging of dilated follicles. Cases have been presented, however, in which the gross appearance of the lesion was that of a morphea-like epithelioma [25] and only after a histopathological examination could the diagnosis of lupus erythematosus be established.

25. Costello, M. J.: Lupus Erythematosus of Unusual Type (Morphea-like Epithelioma?), Arch. Dermat. & Syph. **54**:253 (Aug.) 1946.

In none of our cases did we find an advancing raised nodular border with a self-destructive atrophic center, such as has been described occasionally in the literature.[7] This "field fire" type of epithelioma is, in our opinion, a variety of basal cell epithelioma that should not be included in the group under consideration.

The histopathological features of morphea-like epithelioma are so striking that a section from this tumor should not be confused with one from any other disease. Occasionally, however, a section from ordinary basal cell epithelioma may show a

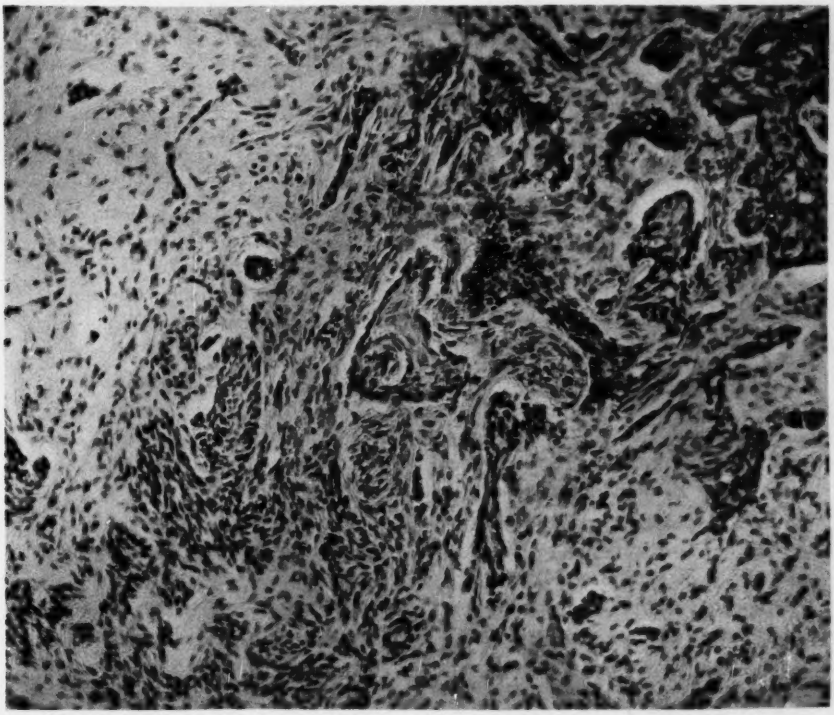

Fig. 9.—Basal cell morphea-like epithelioma, section showing the invading strands of cancer cells surrounded by densely packed connective tissue; hematoxylin and eosin, × 190.

lattice-like arrangement of narrow threads of basal cells. The cancer cells in such cases lie in a loose areolar connective tissue, and they are not separated by the dense fibrous stroma characteristic of morphea-like epithelioma.

TREATMENT

The primary aim in the treatment of any cancer is the total destruction of all malignant cells. In the management of cutaneous cancer the dermatologist has the choice of several methods of treatment, any one of which applied skilfully to

properly selected cases can produce a high percentage of cures. These methods include the Sherwell technic [26] destruction by actual cautery,[27] electrodesiccation, electrocoagulation, excision with the electric knife, surgical excision, roentgen therapy, external or interstitial radium therapy [28] and chemosurgery (Mohs).[29]

In every case the plan for eradicating the cancer should be determined only after a careful evaluation of all pertinent factors, including the age and general health of the patient; the duration of the lesion, its rate of growth, location, size, direction of growth and mobility or attachment to underlying structures; the state of the regional lymph nodes; the previous treatment and its effect, and invariably the diagnosis on the basis of a biopsy. As Michelson [30] stated, "It is a backward step to treat cancer without microscopic confirmation."

Peculiar to morphea-like epithelioma are factors which should influence the kind of treatment selected. Nearly all the lesions of this type occur on the face. Ordinarily the cosmetic result obtained is not an important consideration in the treatment of cancer. In treating a lesion of low grade malignancy on the face, however, it would seem advisable to employ that form of effective treatment which will result in the slightest possible deformity. Because morphea-like epithelioma is seldom diagnosed early, lesions may at times reach a considerable size before coming under treatment. Treatment with roentgen rays or externally applied radium in such cases may result in a large patch of radiodermatitis which not only is unsightly but also may be potentially unsafe.

When the lesion occurs in a location that makes surgical excision feasible, that method has the advantages of instantaneous removal of the tumor, rapid healing after primary closure or skin grafting and often an excellent cosmetic result. There is always the possibility, however, that scalpel excision may be incomplete, and some cancer tissue may occasionally be buried under a skin graft.

The Sherwell technic, even when the curettage is performed vigorously with several curets of progressively decreasing size, is not as effective in this type of growth as in ordinary rodent ulcer. The dense fibrous stroma obstructs the selective removal of the cancerous tissue from the normal underlying base.

Many patients with morphea-like epithelioma have been treated with roentgen rays or externally applied radium. Oliver [31] reported uniformly good results with roentgen therapy, and Senear [32] obtained good results with this treatment, with nothing but a faint scar resulting. Finnerud,[22] however, found these lesions to be

26. Sherwell, S.: Further Observations on the Technique of an Efficient Procedure for the Removal and Cure of Superficial Malignant Growths, J. Cutan. Dis. **28**:487, 1910.

27. Jacobson, H. P., and Alcon, D. N.: Actual Cautery Surgery in Dermatology, Arch. Dermat. & Syph. **61**:842 (May) 1950.

28. Martin, C. L.: The Layer Technique in Radium Needle Therapy, Am. J. Roentgenol. **48**:377, 1942.

29. Mohs, F. E.: Chemosurgical Treatment of Cancer of the Face; Microscopically Controlled Method of Excision, Arch. Dermat. & Syph. **56**:143 (Aug.) 1947.

30. Michelson, H. E.: in discussion on Finnerud.[22]

31. Oliver, E. A.: in discussion on Finnerud.[22]

32. Senear, F. E.: in discussion on Finnerud.[22]

resistant to radiation, as did Montgomery [33] and Traub.[34] In several of our cases treatment by roentgen rays or radium resulted in the healing of the lesion, but in others such treatment was followed by a recurrence of the epithelioma. This apparent discrepancy in the results of radiation treatment may be due to a difference in the size, depth and radiosensitivity of the different lesions.

The interstitial use of radium needles and low intensity radium needles [35] in a few of these cases has been effective. Low intensity radium needles may be used safely when the lesion is located near the eye, on the tip of the nose or near an important organ or tissue.

Chemosurgery is the method of choice in treatment of any lesion that is attached to underlying structures or that is invasive. In all cases of morphea-like epithelioma one can by the use of this treatment successfully remove all malignant cells with the least possible destruction of the uninvolved tissues. This technic, however, requires the skilled collaboration of an experienced operator and a pathologist, and unfortunately it is not available at present to most patients.

A time-honored treatment that has been effective in curing many cases of morphea-like epithelioma is the destruction of the tumor by the actual cautery followed by vigorous curettage of the burned tissue and additional cauterization of the base. The use of the actual cautery may be replaced in this method by electrodesiccation or electrocoagulation, but with the latter modality the destruction is at times deeper than anticipated. Lesions may also be removed by the use of the cutting current and the resulting ulcer be permitted to heal by granulation. Roentgen ray treatments should be administered after any of these measures of local destruction; the dose required to insure against a recurrence of the tumor is small enough to prevent the development of an unsightly radiodermatitis scar.

SUMMARY AND CONCLUSIONS

Thirty-three cases of morphea-like epithelioma were studied, 21 of these being in women and 12 in men. One man had two independent lesions.

The clinical features noted were the occurrence on the face or neck, the gross resemblance of the lesions to morphea except for the telangiectasia on the surface and the frequent eventual ulceration, the slow growth of the lesion and the occasional recurrence after treatment.

The histopathological study showed that 32 of the specimens were basal cell in type and only two were of the prickle cell variety. The tumor was characterized by grouping of the cancer cells into long attenuated strands lying in a dense fibrous stroma. Senile elastosis of varying degree was common to all the sections examined.

Differential diagnosis is given from morphea, localized senile elastosis, lupus erythematosus and "field fire" epithelioma.

Treatment should be individualized in these cases and should be selected only after a careful evaluation of all pertinent factors, both clinical and histopathological.

33. Montgomery, H.: in discussion on Finnerud.[22]

34. Traub, E. F.: Cutaneous Cancer from the Standpoint of the Dermatologist, Arch. Dermat. & Syph. **53**:563 (June) 1946.

35. Howell, J. B.: Cancer of the Center of the Face, South. M. J. **43**:283, 1950.

Dermatologists have the responsibility of making the final diagnosis in most cases of cutaneous cancer. It is equally our responsibility to render an impartial judgment about the kind of treatment most suitable to each case and, except for special technics not at our command, to treat the patient. Finally, we have a duty to the dermatologists who will come after us and to their patients to pass on to our successors our interest in cutaneous cancer and our skill in its diagnosis and treatment. These are obligations we must not abandon.

25 East Washington Street, Chicago 2 (Dr. Caro).

304 Medical Arts Building, Dallas 1 (Dr. Howell).

ABSTRACT OF DISCUSSION

Dr. H. E. Michelson, Minneapolis: Morphea-like epithelioma is a term applied to cutaneous cancer which grossly simulates a small plaque of morphea. However, the lesion of morphea-like epithelioma is yellower and has the characteristics of an epithelioma at the periphery, and there is no ulceration.

What determines the clinical appearance of a cancer? Certainly it is not the microscopic observations. The morphology is altered by the anatomic location, the general character and the care of the patient's skin and, more important, by how the patient reacts to those influences which make his epithelium subject to malignant change. The epidermal cells in their change to cancer cells develop the power to multiply in an abnormal manner and leave the route of their usual growth. As long as the growth is confined to the epidermal boundaries, the cancer is diagnosed as being *in situ*. When the growing power of the cells can overcome the resistance of the surrounding tissues, whether that be cytological or chemical, penetration begins and progresses. In morphea-like cancer, the progress evidently is partially stopped and then growth begins again. As a rule, there is infiltrate beneath an epithelioma, and in this type of cancer Dr. Caro has found some degree of fibrosis. As a rule, there is not much fibrosis except in those cases that have had previous treatment.

One must also be on the lookout for amyloid, which is occasionally found about certain types of skin cancer.

I believe the morphea-like cancer is due to a very low degree of intermittent epidermal proliferation, overcome at times by natural obstruction, only to be taken up again; therefore, there is no spontaneous cure. Its position in a classification of cancer is near that of superficial epitheliomatosis. In Dr. Caro's series the lesions were preeminently basal cell. He reports 6 per cent squamous cell cancers.

As far as therapy is concerned, I would treat these lesions first with radiation and resort to destructive means only if the lesions recur.

I am not positive after looking at the pictures whether I would accept all the cases as morphea-like epithelioma. It is a condition that is not very clearly defined, and each observer has his own ideas as to what constitutes a morphea-like cancer. I feel that the diagnosis is a clinical one and what one observes in biopsy is more or less happenstance. I feel very definitely that there is no microscopic picture for morphea-like cancer, and I doubt that if one saw the slide alone one could diagnose a case as morphea-like epithelioma.

Dr. John F. Madden, St. Paul: It is necessary that we remain cancer conscious. The laity seem to be more cancer conscious than the average general practitioner of medicine. A biopsy should be performed on every lesion that is suspected of being malignant. The microscopic observations confirm the diagnosis and are an aid in instituting proper treatment. We as dermatologists should realize our therapeutic limitations and not try to treat all cancers of the skin and mucous membranes. Occasionally the help of the surgeon or radiologist may mean the difference between life and death to the patient.

Dr. George C. Andrews, New York: I enjoyed this paper very much. I feel as Dr. Michelson does, that if treatment had not been previously given the cases would have been more definite and more acceptable. I feel also as he does, that the treatment by radiation of morphea-like

epithelioma is the best method. But the failure of treatment is not due to the method used but, rather, to the one who uses the method.

Real morphea-like epithelioma is sometimes very difficult to see. The patient may point out a spot, and one may have to look at it two or three times in different lights before one sees it; then, after one does see the spot, one must judge how far it extends outward. Where there is no edge and no definite border, the physician must judge just how far out treatment should go.

I have seen these growths excised by good surgeons with recurrence afterward a centimeter or so outside the line of excision. In other words, epitheliomas extend out into apparently normal skin for a long distance beyond visibility. Sometimes one thinks the lesion extends out a certain distance; then one studies it further and finds that it goes out much farther, even 2 or 3 cm. I think the fault lies in not giving enough extent to the roentgen ray treatment, excision or whatever method employed.

I think these epitheliomas should be treated by dermatologists. I see no reason why they should not be.

Dr. Samuel Ayres Jr., Los Angeles: I think Dr. Caro has pointed out extremely important aspects of cutaneous cancer, and I should like to second Dr. Andrews' remarks about the importance of determining the borders of these lesions. In fact, I refer to these lesions as iceberg type epitheliomas, which expression, I think, indicates their nature. One sees only a comparatively small amount of what is actually present. Not only do they extend down for a considerable distance but also they go outward, often farther than one can see, and it is important to have the very best illumination and put the skin on a stretch; if the new type of skin microscope that Dr. Dennie has told me about is available in the near future, perhaps that will be the answer in determining the borders. Maybe Dr. Dennie will have something to say about that.

Also, the depth of these lesions is sometimes remarkable, particularly in lesions over the malar prominence, as seen here. That site and the forehead seem to be favorite locations for these lesions. My own feeling is that, as far as treatment is concerned, if I had the first chance at it I would prefer to remove the entire area widely and deeply with a high frequency cutting instrument; then under the microscope I could tell pretty well whether I had missed anything.

It has been my experience that irradiation is not as good on these infiltrating types as it is in the case of the elevated types, perhaps because of the sandwiching in of the epitheliomatous tissue between the bands of connective tissue, which apparently act in some manner to protect them.

Dr. Charles C. Dennie, Kansas City, Mo.: Dr. Tassilo Antoine, Chief of the Clinic of Obstetrics and Gynecology, University of Vienna, has recently invented an instrument with which he can perform surface microscopy. This microscope is adapted to examination of the cervix. The microscope, which is lighted within, is inserted into the vagina and the light reflected on the surface of the cervix. One millimeter of tissue can be examined at a time. The cervix is first stained with a vital stain and the instrument inserted. It is possible to revolve the objective and view the whole surface of the cervix. The magnification of this microscope is 200 times. Carcinoma of the cervix follows a certain pattern and can be diagnosed much earlier by the method outlined than by any other method, even more readily than by the Papanicolau staining method. For treatment, cauterization or amputation of the cervix is all that is necessary.

This microscope can be adapted to examination of the skin, I believe, when the vital stain is used on the suspicious lesion. If malignant characteristics exist in the lesion at that time, they can easily be diagnosed by this method.

Dr. Herman V. Allington, Oakland, Calif.: I am sure I have seen this pattern of infiltrating basal cells surrounded by pronounced fibrosis in a number of cases of morphea-like epithelioma without previous treatment. Secondly, I agree that treatment should be fitted to the individual case. I do not think that these lesions lend themselves to curettage and electrodesiccation in the way the ordinary basal cell epithelioma does, probably because the fibrosis makes the

lesion firm and resistant to the curet. It is not friable, as basal cell epitheliomas usually are. I believe many of these lesions should be removed by sharp excision and carefully marked so that sectioning may be done in several well identified planes. In this way one may attempt to determine whether or not adequate margins have been allowed.

DR. L. H. WINER, Beverly Hills, Calif.: I wish to compliment Dr. Caro on his excellent paper dealing with a subject of importance to all of us.

The tendency of a neoplastic growth to stimulate fibrosis is frequently observed in slow growing basal cell carcinoma but rarely observed in a prickle cell carcinoma. In the latter, cellular infiltration of an inflammatory nature is a more prominent feature.

The fibrosis in the morphea-like basal cell carcinoma has practically no associated cellular inflammatory reaction. Histologically it gives one the impression of a noninflammatory hypertropic scar permeated by nests of proliferating epithelial cells. It suggests nature's attempt to wall off a slow growing lesion. On the other hand, this self-induced curative process complicates therapy because the proliferating epithelial cells are shielded by the dense scar formation.

The negative observations in the tissue stained for calcium were interesting. We have assumed that the degeneration of the collagen is associated with a deposition of calcium indicated by the increased depth of blue at the outer border of the collagen fasciculi in sections stained with hematoxylin and eosin. Apparently, according to the results of staining in the present study, this material is not calcium.

DR. G. MARSHALL CRAWFORD, Brookline, Mass.: A few months ago one of our residents at the Massachusetts General Hospital discovered by accident that this type of morphea-like epithelioma could be rather neatly outlined on examination with the Wood light. Since that time we have used this technic more extensively for other superficial lesions. This will not differentiate them, but one can be surprised by the extent of the change that shows up under the Wood light.

The favorite method of treating epitheliomas employed by one of our older colleagues was curettage followed by the application of nitric acid. I do not use that method but since his retirement have seen many of the patients he treated without a single recurrence.

That fact and the remarks of Dr. Andrews and others bear out the point that the important thing is not so much the manner of approach to these lesions as the thoroughness with which treatment is applied and the allowance of adequate margins.

DR. MARCUS R. CARO, Chicago: I am grateful to Dr. Michelson for assuming the task of opening the discussion of this paper on such short and inadequate notice. I also wish to thank all the other discussers for their comments and contributions. I must disagree with Dr. Michelson on at least two points. In our paper we give ample evidence that the clinical appearance of the lesion in morphea-like epithelioma is due entirely to the histopathological features that are present. The histopathological basis for the flat and saucer-like appearance with no nodular border was well demonstrated in the illustration from the section of Dr. Wile's case, showing a shallow flat band of carcinoma cells lying in a sclerotic corium just beneath the epidermis. As for the suggestion of the presence of amyloid, we did not examine any of these sections with the congo red stain, but we did employ the Van Gieson stain in many of the specimens. In cases of amyloidosis I have been able to demonstrate the presence of amyloid by the use of this stain. In our sections of morphea-like epithelioma the Van Gieson stain showed the collagen fibers to be present and well stained even in the areas of senile elastosis, and in none was there any suggestion of the presence of amyloid.

Concerning the statement that it would have been better to present patients who were not treated before, most of the lesions illustrated here had not received any previous local treatment at all or had not received any treatment to the site of the present lesion.

The large patch on the cheek of the woman had been present for 10 years. It had been repeatedly diagnosed as morphea, and it had not been treated. The ulcer in the patch was spontaneous and not the result of previous irradiation or any other destructive measure. The case of involvement of the neck showed recurrences in areas of skin that were previously untreated, both above and below the scar of the original cancer. The patient with the cancer on the temple was untreated.

I am glad to know about the suggestion of Dr. Dennie's concerning surface microscopy, and I shall be glad to use the Wood light in all the cases I see in the future, although the border of morphea-like epithelioma may be delineated accurately also by palpation.

In the presidential address that opened this meeting Dr. Dennie made reference to the dying syphilologist, and he deplored the trend that is replacing the mature clinician with a combination of the untrained investigator and the statistician with nimble fingers. The papers read since then have given ample evidence that the men who pioneered our specialty have been followed by a generation that is mindful of its great heritage and is conscious of its responsibility to our successors. We must continue to give proof by our work that the dermatologist is the one best qualified to pass final judgment as to the diagnosis and treatment of all diseases of the skin, including cancer. I must disagree with Dr. Madden in his remark that we are not qualified to treat skin cancer. Some of these cancers, it is true, may require technics with which we are not familiar or which we do not have at our command. The dermatologist, however, should be the one who is responsible for the diagnosis, for the decision as to the type of treatment most suitable and, whenever possible, for the treatment of cutaneous cancer.

TRANSVERSE NASAL STRIPE AT PUBERTY (STRIA NASI TRANSVERSA)

THEODORE CORNBLEET, M.D.
CHICAGO

ALMOST two years ago I saw a child with a peculiar streak straddling her nose. It was about a millimeter in width and about where the middle and lower thirds of the nose join. It was rose red and straight and lay athwart the nose. The child complained of no symptoms, nor was there tenderness. The mother said she had noticed the linear formation for several months—from the time her daughter was 10 years old. Sometimes it stood out more and then paled; it did not entirely fade.

About five months later, I chanced to see a similar lesion on a girl of 12. This observation was a coincidence, as the child came to me because of some other disorder. The mother said that the streak might have been present for some months, but she was not sure (it did not concern her much). In every way the streak astride the nose of this girl was similar to the first one described.

In all, in two years I have seen five children with this peculiar cross streaking between the middle and lower thirds of the nose (this observation does not indicate the incidence of the lesion because I treat relatively few children); none of them except the first came to me because of it. All these patients were girls before or near puberty.

Three of them have begun to menstruate, and all except one with eczema seem to be normal in every way. The striping goes through a periodic waxing and waning, but I have seen no exact rhythm to it (such as would occur within a menstrual cycle). The intensity of the color finally recedes as the girls mature past puberty.

Besides color, there is another feature—a faint troughing. It is not a real depression but rather a kind of angulation—enough to develop a fine shadow. This drew my attention to a closer observation of the entire tip of the nose in children and what happens to it as they mature.

I noted that children have round nostrils before they are 10 years old or thereabouts. Gradually this circle becomes ovoid and then elliptic.

From the Departments of Dermatology, University of Illinois College of Medicine, Dr. F. E. Senear, chief, and the Cook County Hospital.

Fig. 1.—Nasal stria in girl with eczema.

Fig. 2.—Usual appearance of nostrils.

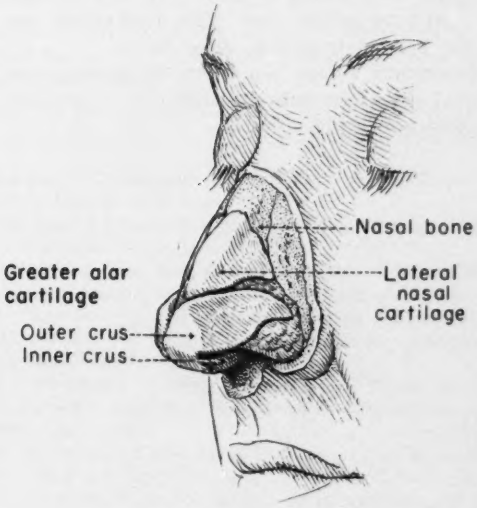

Fig. 3.—Cartilages of the nose.

The nostril continues to elongate from front to back until adolescence. (The nose really continues to change its form throughout life into old age, but we are not concerned with that point here.)

There are reports and reviews in the anatomic, rhinologic and pediatric literature on the development of the nose and sinuses in the embryo and in childhood that are excellent and detailed. Nowhere have I seen any reference to the changes in the distal part of the nose around puberty. Yet there are obvious ones (even if only the shape of the nostril is considered).

The shape of the nostril really depends on that of the two major alar cartilages and the lower end of the septal cartilage as it juts forward for all three to join. It is easy to feel how these cartilages thicken and mass as children approach puberty.

It seems that the growth of these cartilages at this time trusses up the entire end of the nose. This forms a kind of faint crease (it amounts to more in some cases) between the middle and lower thirds. A few children acquire a rose red coloring at this site that gives the appearance of a reddish stripe across the nose. I do not know whether this development ever occurs in boys, but I have never seen it in them.

SUMMARY

I have seen five girls with a peculiar reddish streak across the nose. It is a narrow line that lies where the middle and lower thirds join. It forms when the lower nasal cartilages develop before puberty to truss up the lower end of the nose (there is a simultaneous change in shape of the nostrils). This pushing out and up of the lower end of the nose angulates it with the middle third. This development may explain in part how the peculiar transverse stripe forms.

This phenomenon, I think, is a variety of "growing pains," in which the distal part of the nose enlarges faster than its adjacent portion, to produce a reddened line of distortion.

EPITHELIOMA ADENOIDES CYSTICUM: BASAL CELL NEVI, AGENESIS OF THE CORPUS CALLOSUM AND DENTAL CYSTS

A Clinical and Autopsy Study

GEORGE W. BINKLEY, M.D.
AND
H. H. JOHNSON Jr., M.D.
CLEVELAND

THE PRIMARY purpose of this paper is to present features of epithelioma adenoides cysticum which have not usually received adequate attention from dermatologists. From the earliest articles by Brooke [1] and others,[2] through that by Savatard [3] down to the most recent reports, the congenital defects associated with this disease have not been commented on or have received only brief mention.

Recently we had the opportunity to observe a patient with lesions of epithelioma adenoides cysticum who also presented other developmental anomalies constituting a bizarre clinical picture. In addition to the cutaneous lesions there were partial agenesis of the corpus callosum (discovered at autopsy) and multiple dental follicular cysts. The latter proved to be the most serious condition, for a fibrosarcoma of the mandible appeared and metastases caused the patient's death. The patient also had mesodermal anomalies consisting of a bifid sixth rib and a fibroma of the ovary.

We were unable to discover a previous similar case. However, our case is reminiscent of epiloia [4] with its multiple congenital malformations, and it probably should be placed in the group of conditions in which cutaneous anomalies are part of a widespread congenital defect.

Morphological and histological [5] variations in the lesions have been noted. In 1904 Hartzell [6] stated that cylindroma of the scalp, epithelioma adenoides cysticum

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From the Department of Dermatology and Syphilology, Western Reserve University School of Medicine, Harold N. Cole, M.D., director.

Read at the Seventieth Annual Meeting of the American Dermatological Association, Inc., Jasper National Park, Alberta, Canada, June 19, 1950.

1. Brooke, H. G.: Epithelioma Adenoides Cysticum, Brit. J. Dermat. **4**:269 (Sept.) 1892.

2. (*a*) Fordyce, J. A.: Multiple Benign Cystic Epithelioma of the Skin, J. Cutan. & Genito-Urin. Dis. **10**:459 (Dec.) 1892. (*b*) Jarisch: Zur Lehre von den Hautgeschwülsten, Arch. f. Dermat. u. Syph. **28**:163, 1894. (*c*) White, J. C.: Multiple Benign Cystic Epithelioma, J. Cutan. & Genito-Urin. Dis. **12**:477, 1894.

3. Savatard, L.: Epithelioma Adenoides Cysticum, Brit. J. Dermat. **34**:381 (Dec.) 1922.

4. Butterworth, T., and Wilson, M.: Dermatologic Aspects of Tuberous Sclerosis, Arch. Dermat. & Syph. **43**:1 (Jan.) 1941.

5. Goldman, H. G.: Multiple Benign Cystic Epithelioma, J. A. M. A. **115**:2253 (Dec. 28) 1940. Lever, W. F.: Histopathology of the Skin, Philadelphia, J. B. Lippincott Co., 1949.

6. Hartzell, M. B.: Benign Cystic Epithelioma, and Its Relationship to So-Called Syringocystadenoma, Syringocystoma, and Hemangioendothelioma, Brit. J. Dermat. **16**:361, 1904.

and syringoma are all varieties of trichoepithelioma. The occurrence of multiple cystic epithelioma with syringoma in the same patient has been reported by Sutton and Dennie [7] and by Ingels.[8] In the cases reported by Jarisch [2b] and by White [2c] some of the lesions were ulcerated, and Adamson [9] in 1908 advanced the opinion that there was possibly a relationship between epithelioma adenoides cysticum and rodent ulcer. The relationship between epithelioma adenoides cysticum, trichoepithelioma and basal cell carcinoma was discussed by Traenkle.[10] We believe that the cases reported by Nomland [11] and Nesbit [12] as "multiple basal cell epithelioma originating from congenital pigmented basal cell nevi" and those reported by Pautrier and Archambault [13] belong with this group.

Pautrier and Archambault reported five histological variations of epithelioma in their patient, who had more than 200 widely distributed lesions, all of the benign basal cell type. In our case, the clinical appearance of the lesions varied and histological examination of different lesions revealed significant differences. Some had the characteristics of epithelioma adenoides cysticum, and others had the features of basal cell epithelioma, some with ulceration. A natural conclusion would be that the latter were the older lesions, representing a transformation from the earlier benign lesions, but this should not be assumed in view of the multiplicity and wide distribution of the tumors. Since variations of this kind have been reported so frequently, it may be that these are morphological variants of the skin condition resulting from the congenital defect. Although Cockayne [14] cites a few instances in which malignant degeneration of lesions reported as epithelioma adenoides cysticum resulted in generalized metastases, these tumors as a rule are only locally malignant. This statement is also true for the cases which have been reported as multiple epitheliomatosis and basal cell epithelioma arising from congenital pigmented nevi.

REPORT OF A CASE

The patient, a white woman aged 30, was referred to us by Dr. Gerald S. Shibley. Her chief complaints were swelling of the right portion of the mandible and growths of the skin.

7. Sutton, R. L., and Dennie, C. C.: Possible Interrelationship of Acanthoma Adenoides Cysticum (Multiple Benign Cystic Epithelioma) and Syringocystadenoma (Lymphangioma Tuberosum Multiplex), J. A. M. A. **58**:333 (Feb. 3) 1912.

8. Ingels, A. E.: Epithelioma Adenoides Cysticum with Features of Syringoma, Arch. Dermat. & Syph. **32**:75 (July) 1935.

9. Adamson, H. G.: Two Cases of Multiple Rodent Ulcer, with a Note on the Possible Relationship Between Multiple Rodent Ulcer and Epithelioma Adenoides Cysticum of Brooke, Lancet **2**:1133, 1908.

10. Traenkle, H. L.: Epithelioma Adenoides Cysticum, Trichoepithelioma and Basal Cell Cancer: Relationship Between These Diseases, as Shown by Histologic Studies of Multiple Benign Cystic Epithelioma, Arch. Dermat. & Syph. **42**:822 (Nov.) 1940.

11. Nomland, R.: Multiple Basal Cell Epitheliomas Originating from Congenital Pigmented Basal Cell Nevi, Arch. Dermat. & Syph. **25**:1002 (June) 1932.

12. Nesbit, T. W.: Multiple Basal Cell Epitheliomas Originating from Congenital Pigmented Basal Cell Nevi, Arch. Dermat. & Syph. **47**:373 (March) 1943.

13. Pautrier, L. M., and Archambault, G.: Extraordinary Case of Cutaneous Epitheliomatosis: More Than 200 Epitheliomata Appearing over 23 Years on the Entire Skin, Without Metastases, and Showing 5 Histologic Variations, Bull. Assoc. franç. p. l'étude du cancer **16**:835 (Dec.) 1927.

14. Cockayne, E. A.: Inherited Abnormalities of the Skin and Its Appendages, London, Oxford University Press, 1933.

Her father was living and well, with no cutaneous malformations; her mother had died at age 34 of gallbladder disease, and there was no history of cutaneous growths. She had one sister living and well. The patient had five children, ages 7, 6, 5, 4 and 2 years. All were given cutaneous and dental examination; only one, a girl aged 6, showed epithelioma adenoides cysticum.[15]

A "fatty" tumor of the left foot had been removed twice when the patient was aged 14. When it was removed a second time, permanent cure resulted. No histological report could be obtained. When the patient was aged 18 an appendectomy was done. At this operation a tumor of

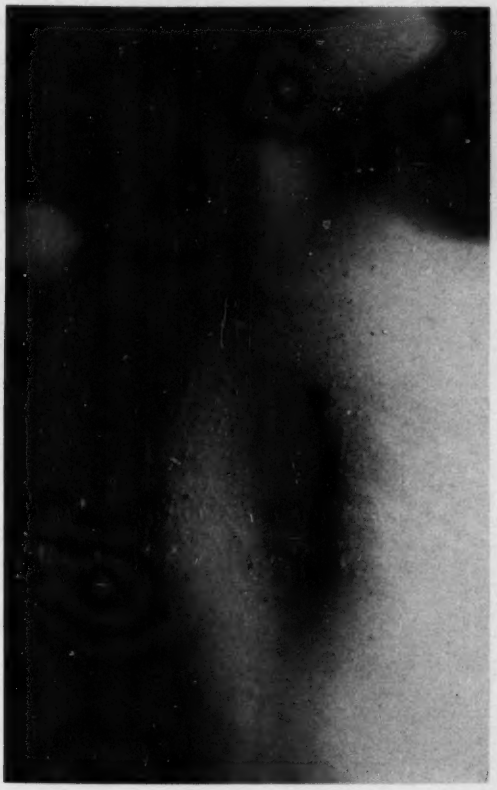

Fig. 1.—Many small papules on the neck and chest of the patient's daughter, aged 6.

the left ovary was removed. The pathological diagnosis was fibroma, the seat of extensive necrosis.

15. This child had many small round papules, varying in color from that of normal skin to a pale brown. They were located on the face, chest, axillas and groins (figs. 1 and 2). Roentgenograms of the skull, sinuses, mandible and chest revealed no disease of the bones or teeth. A psychometric examination revealed normal mentality. Histological examination of skin from the sternal area showed the same changes as were found in a biopsy of a specimen from the mother. There were branching columns of basal cells and small cysts, and in some instances the cell masses were related to hair follicles. The individual cells were oval or fusiform, the nuclei sharply defined. Superficial roentgen therapy of 1,800 r had slight effect on the papules.

At age 16 the patient had consulted a dentist because of persistent swelling of the right side of the mandible. Roentgenologic examinations[16] revealed multiple dental follicular cysts in both sides of the mandible with expansion of the cortex of the entire right portion. There were unerupted permanent teeth. There was a tooth seemingly located in the right antrum (figure 3).

An attempt was made to control the enlargement of the cysts or tumors by roentgen irradiation from 1934 through 1941. The patient was admitted to the hospital in January 1949 for treatment of the tumor of the mandible and the cutaneous growths.

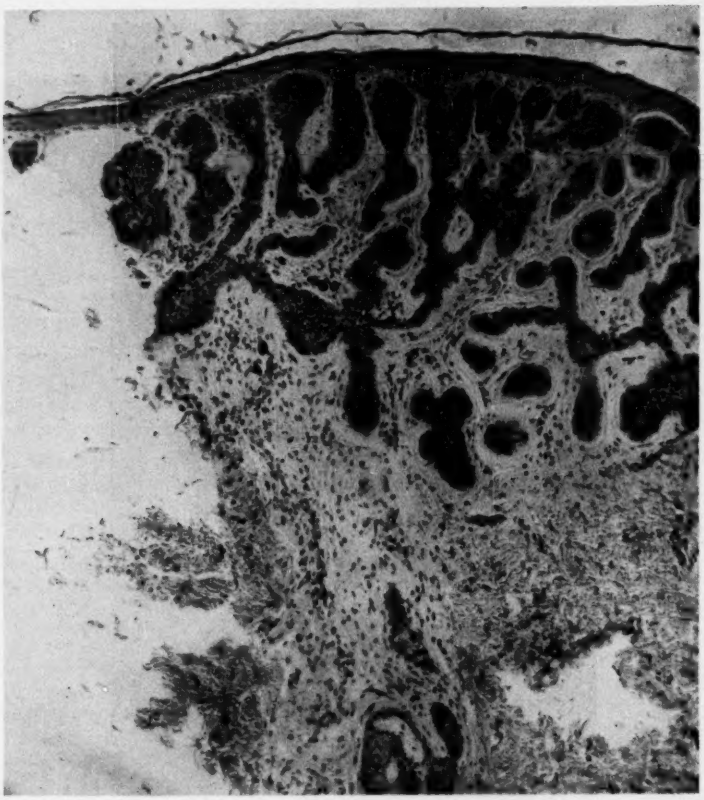

Fig. 2.—Histological changes of a papule from the skin of the sternal area, site visible in figure 1. Strands of interconnecting basal cells and pigment in macrophages may be observed.

About three cutaneous growths were recorded by an examiner in March 1937. They were located on the chin and below the right eye. A total of 5,000 r of superficial irradiation was given to three small areas in 1941 for cutaneous ulcerations. One field included the lower lip and chin; another, the right cervical region, and another, an area of the upper part of the back.

The patient was a well developed, mentally dull white woman. She was 161 cm. in height and weighed 54.4 Kg. There were innumerable (estimated number, more than 1,000) slightly

16. We wish to acknowledge the loan of roentgenograms from Dr. R. A. Snelson, Dr. E. C. Baker and Dr. H. M. Weber.

raised, hard papules, 1 mm. to 1 cm. in diameter, situated on the face, neck, anterior and posterior portions of the chest and the proximal portion of the arms (fig. 4). The same types of lesions were present over the lower part of the thoracic region, the abdomen and the lumbar area. Small papules were found in the axillas, suprapubic and inguinal regions and in the scalp. Some of the scalp lesions were olive sized. A hard oval tumor, 3.0 cm. in diameter, was present in the left posterior auricular region.

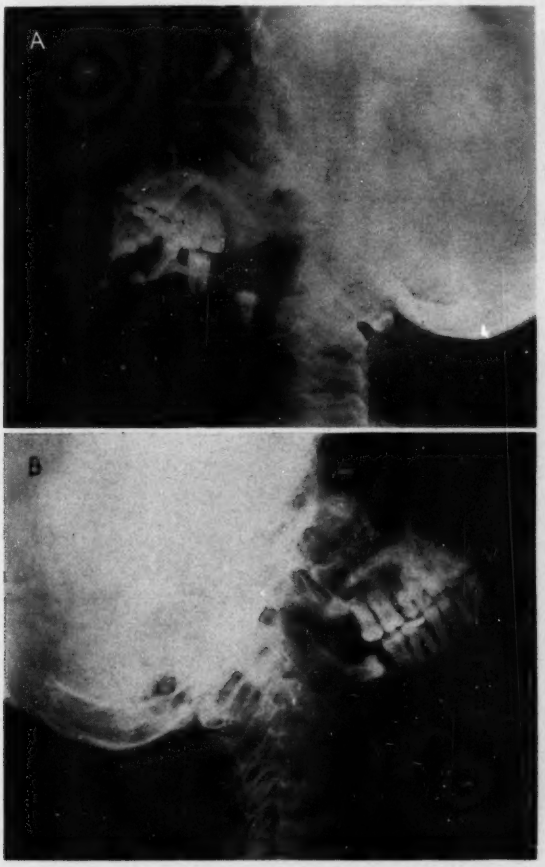

Fig. 3.—*A*, multiple dental cysts involving the entire right side of the mandible. *B*, dental cysts of the left portion of the mandible. Note the unerupted tooth "in the antrum."

Two ulcerated lesions on the face measured 1 and 2 cm. in diameter. They had indurated, elevated pearly borders. The entire right side of the neck was erythematous. There was hyperpigmentation, telangiectasia and atrophy of the skin over the right portion of the mandible and the neck at sites of previous irradiation.

The entire right side of the mandible was enlarged. There was limitation in movement of the temporomandibular joint. Only four lower incisor teeth could be seen (fig. 5).

A roentgenogram showed an extensive area of osseous destruction involving the right horizontal ramus of the mandible. In the sinus view the lower wall of the right antrum was destroyed and an area of increased density extended into the right maxillary sinus, almost obliterating it. In the center of the dense area was a tooth, located near the upper posterior wall of the right maxillary sinus. A roentgenogram of the chest revealed that the anterior end of the right sixth rib was bifid. The hemogram and results of urinalysis were normal. In July, two months before the patient's death, sternal bone marrow revealed large clumps of tumor cells. As the disease

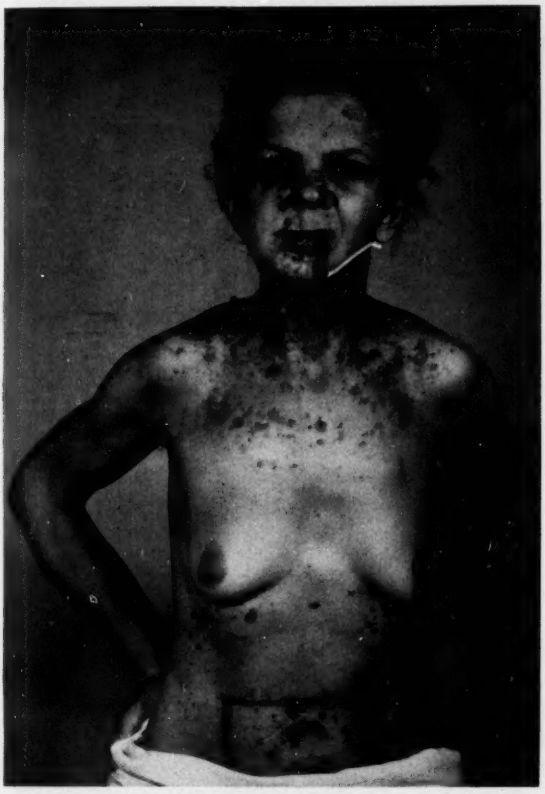

Fig. 4.—Distribution of lesions, sparing breasts and distal portions of the upper extremities. Note the ulcerated epitheliomas on the face. There is a radiodermatitis of each side of the neck.

progressed there was evidence of anemia (3,650,000 erythrocytes) and a leukemoid reaction (40,000 leukocytes) shortly before death.

Histological examination of a lesion from under the right eye showed many nests of poorly defined cells having pale cytoplasm. There was palisading of the cells (figs. 6 and 7) at the periphery of the nests. A papule from the left shoulder showed large, irregularly shaped masses of poorly defined cells with a palisaded border. The corium was infiltrated with lymphocytes and scattered macrophages containing brown pigment. The histological observations in skin from the upper back were the same as those described above except that the masses were large and well defined and contained numerous small cystlike spaces. Microscopic study of an ulcerated

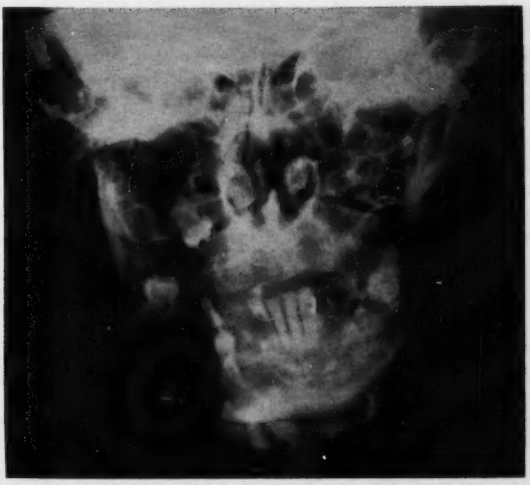

Fig. 5.—Roentgenogram showing progression of the fibrosarcoma, destroying the right side of the mandible.

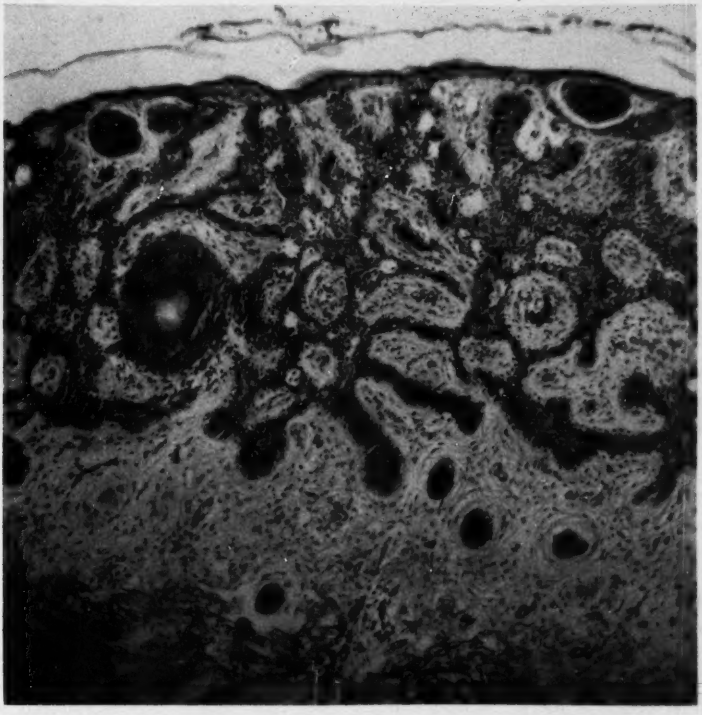

Fig. 6.—Strands of connecting basal cells showing origin from the epidermis and hair follicle. Pigment masses are present in the corium. These features may be compared with the histological picture of a lesion from the patient's daughter (fig. 2).

growth showed that the dermis contained cells resembling basal cells. The cell masses contained numerous round spaces of varying size, in some of which there was a loose fibrillar network. The border cells were palisaded. Mitotic figures averaged one to two per high power field. The epidermis was ulcerated in one field.

Histological examination of bone from a hemiresection of the right side of the mandible showed fibrosarcoma. Additional therapy to the cutaneous lesions included irradiation, interstitial radium treatment, cryotherapy with solid carbon dioxide and excision of scalp lesions.

An autopsy showed widespread dissemination of the fibrosarcoma. The metastases, which were proved microscopically to be fibrosarcoma, were found in bone, skull, ribs, vertebral column

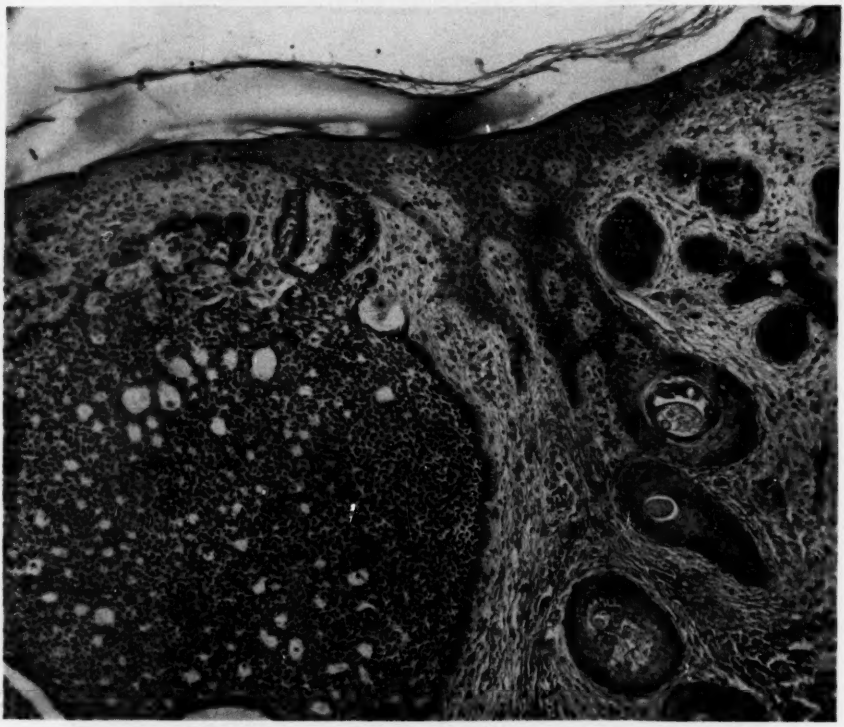

Fig. 7.—A large basal cell mass with many small cysts, horn cysts and strand type growth.

and many viscera. Microscopic study of the various organs revealed no evidence of metastases from epithelial growths. An unsuspected lesion was a partial agenesis of the corpus callosum (fig. 8).

COMMENTS

In a review of the literature on epithelioma adenoides cysticum, two observations stood out: that there are histological variations in clinically similar lesions and that there is a lack of detailed information regarding the other genetic defects which accompany this disease. Although Savatard [3] reports the dermatologic observations in great detail, he merely mentions in summary that "other congenital defects were present in many of these cases." Savatard reviewed the literature to 1922, and the

report by Summerill and Hutton [17] included a review of the literature to 1932. Cockayne [14] also presented a review of the subject in which, on the basis of a compilation of reports of cases, he stated that the disorder is inherited as a dominant characteristic but with a definite though partial limitation to the female sex. Fliegelman and Kruse [18] examined 22 members of three generations of a family. Eight had

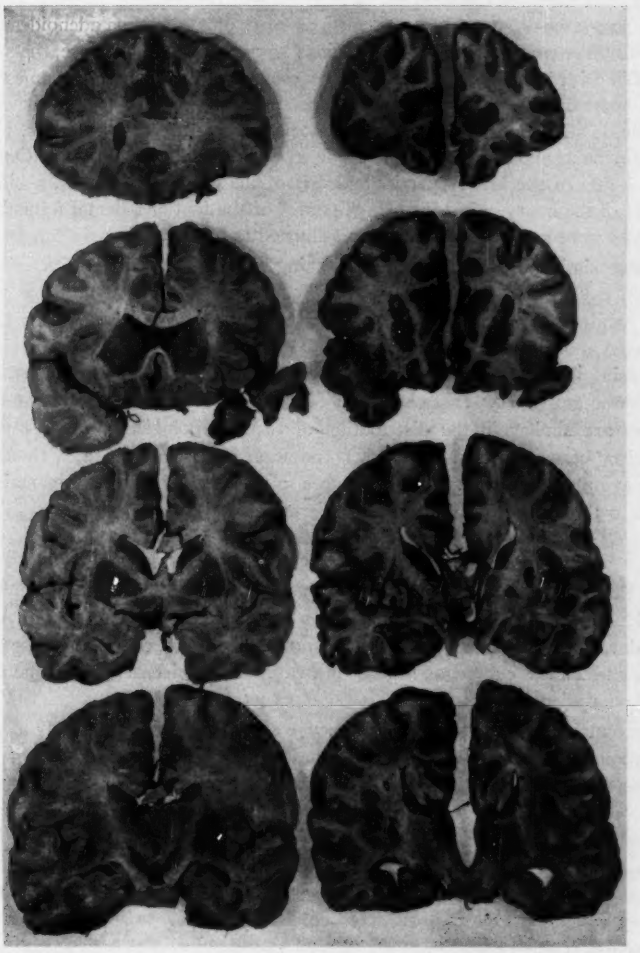

Fig. 8.—On the left side, a normal brain; on the right side, the patient's brain, showing the partial agenesis of the corpus callosum.

17. Summerill, F., and Hutton, J. G.: Multiple Benign Cystic Epithelioma (Epithelioma Adenoides Cysticum) with Summary of Literature, Arch. Dermat. & Syph. **26**:854 (Nov.) 1932.

18. Fliegelman, M. T., and Kruse, W. T.: Hereditary Multiple Benign Cystic Epithelioma, J. Invest. Dermat. **11**:189 (Sept.) 1948.

multiple benign cystic epithelioma. The criteria of dominant inheritance were fulfilled, but there was no evidence of sex limitation in this family.

We were unable to compare the observations in our case with those in other cases of epithelioma adenoides cysticum. Jarisch [2b] reported that his patient was short and of "weak constitution," with low intelligence and a high grade scoliosis. Our patient was short and small, apparently dull mentally.

Although we did not find any reports on cases of epithelioma adenoides cysticum in which there were as many malformations as there were in our case, the syndrome of epiloia with its many ectodermal and mesodermal malformations comes to mind for comparison. In this condition, the cutaneous lesion, which may be single or multiple, is adenoma sebaceum and is associated with tuberous sclerosis, phakoma, rhabdomyomas and fibromas of the kidneys, skin and subungual tissue. Our patient had a lesion of the brain (partial agenesis of the corpus callosum), a bifid rib, a fibroma of the ovary, a history of a "lipoma" of the foot and dental follicular cysts. The eyes were carefully examined and showed no abnormality.

These similarities do not prove anything as to the existence of a relationship between epiloia and epithelioma adenoides cysticum but suggest that it might be worth while to compare these and other hereditary diseases in which there are associated anomalies of several systems. The ophthalmologist, J. Van der Hoeve,[19] introducing the phakomatoses, has done just that. He combined tuberous sclerosis, neurofibromatosis, von Hippel-Lindau disease and Sturge-Weber disease. These diseases are similar in the distribution of their pathological processes and their familial or hereditary character. Each condition is clinically distinct, though many of the symptoms overlap. The differences in these phakomatoses are mainly with regard to the type of cell showing proliferation.

SUMMARY

In this report of a woman with the history and manifestations of epithelioma adenoides cysticum, special emphasis has been placed on a discussion of many other developmental defects which were found. These associated anomalies and the finding of identical cutaneous lesions in a daughter emphasize the genetic origin of epithelioma adenoides cysticum.

The cutaneous lesions, although they were numerous and widely distributed and although some lesions were ulcerated and showed local malignant degeneration, did not present the major clinical problem. The dental follicular cysts of the mandible eventually degenerated into fibrosarcoma with widespread metastases and death. A third condition was discovered at autopsy—a partial agenesis of the corpus callosum. In addition to this major triad of anomalies the patient had a fibroma of the ovary, removed when she was 18, and a bifid sixth rib. There was a history of a "fatty tumor" of the foot, which may possibly have also been a fibroma.

Discussion of the noncutaneous picture has been presented with the hope that it might contribute to our knowledge of the general group of hereditary diseases in which cutaneous tumors are a single feature of a generalized disorder.

19. Van der Hoeve, J.: Doyne Memorial Lecture: Eye Symptoms in Phakomatoses, Tr. Ophth. Soc. U. Kingdom **52**:380, 1932.

ABSTRACT OF DISCUSSION

DR. HARTHER L. KEIM, Detroit: I feel Dr. Binkley has done us a real service in calling our attention to the frequency that we dermatologists overlook or, shall I say, do not look for other signs and symptoms of this group of diseases. This particular patient strikingly emphasizes this fact. She had 1,000 or more cutaneous lesions, but they were not her chief concern. She died of something else—of malignant degeneration of the follicular cysts in the mandible.

In like manner it is my feeling that we have been too busy attempting to find and record minute microscopic variations and that too much emphasis has been placed on differentiation. I believe the need now exists for an attempt to stress the similarities and interrelationships of this group of nevoid diseases. I am thinking particularly of multiple benign cystic epithelioma, syringocystadenoma, adenoma sebaceum and neurofibromatosis, all hereditary syndromes, all presenting interrelated clinical features, all appearing most frequently at puberty, all arising from embryonal cell rests and all frequently showing associated osseous or nervous system involvement. In fact, about the only dissimilarity to be found is in the microscopic pictures, and many times there is disagreement about even this feature by those who record cases.

I feel, too, that we are all in agreement that our students find terminology in these diseases particularly confusing, which difficulty would be obviated if in our teaching we grouped these diseases and stressed the similarities rather than trying to ferret out questionable differences. Further, I think we should emphasize the common hereditary features and investigate the genetic background. Certainly, epithelioma adenoides cysticum is to be regarded as a hereditary disease in light of past reports, notably one made about 10 years ago by Goldman, who found 10 examples in one family, and more recently one by Fliegelman and Kruse, who on examining 22 members of one family found eight individuals so affected and two others reported to have had the disease. This last-mentioned family is of further interest because a number of its members presented *café-au-lait*-like spots, usually held to be characteristic of neurofibromatosis.

I did enjoy Dr. Binkley's presentation and hope he will avail himself of the opportunity of following the children of his patient at least through their adolescent years.

DR. FRED S. WEIDMAN, Philadelphia: This subject is in the realm of congenital abnormalities, in the final analysis. One point to this presentation has been that it indicates a greater range of abnormalities which may take place in this disease than is usually thought of. Thus, all of us are familiar with the usual assemblage of tissue changes which are charted for the clinical and microscopic characteristics, but in the case reported here the congenital abnormalities extended (histologically) far beyond those which we are familiar with, even to such extremes as the formation of cysts and the development of what amounts to basal cell cancer. The extreme ulceration of the lesions in this case must be a manifestation which we would ordinarily regard as of basal cell cancer. I want to support Dr. Binkley's and Dr. Keim's contention that their claims are not vitiated simply because the histologist confuses a basal cell cancer with a congenital multiple epithelioma.

When I saw the first slide on the screen I thought, "That is simply a basal cell cancer," and perhaps Dr. Becker thought that it might represent the reticular type of seborrheic keratosis, on which he will present a paper later at this meeting. But the point to keep in mind, which supports Dr. Binkley's thesis, is that there is a very wide range of histological changes possible in multiple benign cystic epithelioma.

In many of the cysts there is not any clearcut relationship to the hair follicles. Histologically this complicated nevus is more like basal cell cancer than anything else, as Traenkle brought out and concerning which point the elder Mallory many, many years ago started us on the right path. I dare say that if, instead of one biopsy, 20 biopsies had been done, a lesion would have been found in which the typical histologic picture was exhibited.

DR. L. H. WINER, Beverly Hills, Calif.: I enjoyed this paper very much, because it emphasizes the features which general pathologists ascribe to epithelioma adenoides cysticum, namely, the tendency to form small cavities and cysts. However, I have always contended that in epithelioma adenoides cysticum there should be, in addition, keratinous contents in these cysts, free-lying keratin in the cutis and solid masses of epithelial cells.

Occasionally there is malignant degeneration, but even in malignantly degenerated epithelioma adenoides cysticum there is also free keratin as well as keratin within epithelium-lined cysts.

Of further interest in this case was the tendency of the bone lesions to form cysts. Were these cysts, or were they replacement of bone by the growing tumor?

Dr. George W. Binkley, Cleveland: Unfortunately there were no biopsies of the dental lesions from age 14 to age 30, and so we do not know whether the cysts were benign originally or whether the lesion was fibrosarcoma from the beginning. I am inclined to the view that the original lesions were dental follicular cysts with fibrosarcoma eventuating in one or more of the jaw lesions.

The so-called adenoma sebaceum of the syndrome tuberous sclerosis is often a misnomer. Histological examinations of the facial lesions of tuberous sclerosis may show trichoepitheliomas. In the Sturge-Weber syndrome, the involvement of the skin may include syringoma in addition to the angiectasis. A patient in our clinic had eye and brain lesions, polycystic kidneys and syringoma of the skin of the neck.

A STUDY OF SYPHILIS IN NORTHERN ALBERTA

HAROLD ORR, M.D.
AND
PAUL L. RENTIERS, M.D.
EDMONTON, ALBERTA, CANADA

SINCE 1943, when Mahoney, Arnold and Harris first reported on the use of penicillin in the treatment of syphilis, many excellent papers have been presented dealing with the efficacy of various dosage schedules in the different manifestations of the disease. It is not our purpose in this discussion to add to these reports but rather to present information concerning a problem in the management of syphilis in northern Alberta and the manner in which it is being attacked.

The syphilis rate amongst the white population in this province has recently been extremely low, varying from 0.7 per 1,000 in 1945 to a present rate of 0.3 per 1,000. Two spot surveys, one in 1921 and one in 1935, had disclosed no evidence of syphilis in the population of northern Alberta in excess of that in the inhabitants of the province as a whole. However, during the early days of World War II and with the construction of the Alaska Highway it was soon noticed that the Indian and métis, or half-breed, population in northern Alberta was serving as a nidus of infection, not only for the sparse civilian population of the area but also for the American and Canadian armed forces stationed or transient along this route. It was further noted that the greater problem existed along the first 400 miles of the route, that is to say, between Edmonton and Peace River. One must realize that this part of the highway runs through at least 300 miles of near wilderness broken only here and there by small villages, the inhabitants of which are in large part Indian or "breed" (métis). The population is in no way fixed. These people are true nomads and will disappear for months at a time into the forest and lake country surrounding these hamlets. In fact, they may never reappear in the same village but may wander hundreds of miles to some other "camp," taking with them their entire families and all their possessions.

Needless to say, medical and nursing facilities in this territory were meager. In the greatest danger zone there existed a 200 mile stretch entirely without medical aid. The low moral standards of the Indians, their general illiteracy and their acceptance of aliases and nicknames all added to the difficulty of venereal disease control amongst them.

However, in 1944, with the support of both provincial and federal health authorities, mass blood testing of the inhabitants of an area covering 40,000 square miles was begun. The task required 14 months for completion, as winter travel was practically impossible and even during the summer months many encampments could be reached only by saddle horse or wagon travel. By the summer of 1946

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all preliminary work was completed and as the result of a total of 1,300 blood tests taken, 145 patients (111 per 1,000) were found to have positive serologic reactions (Kolmer and Kahn tests). It was, of course, impossible to determine the number of biologic false positive serologic reactions in this group, and it was decided that all 145 patients should receive treatment.

In September 1946 all 145 patients were brought together in a "military type" tent camp situated at the northwestern tip of Lesser Slave Lake, and on second testing all but six were found to be still serologically positive. Their attendance was largely voluntary and had been assured by the simple expedient of the offering of free food and camping wherewithal. As the Indian will never travel without his family, the camp personnel soon found facilities taxed to the breaking point. Instead of the original number intended, the camp soon contained in the neighborhood of 350 men, women and children. The typical Indian family listed not only parents and children but also in many cases grandparents, uncles and so on, who "came along." The inevitable sled dog population only served to make the camp typically Indian. The patient population consisted of 89 females and 56 males ranging in age from 1 to 70 years, with the average age of the group set at 33.5 years. Cerebrospinal fluid examination was done on all but 14 patients, examination being withheld in these cases either because of the patients' advanced age or because of pregnancy. Thus 137 patients revealed a positive serologic reaction only whilst eight patients revealed positive reactions of both blood and cerebrospinal fluid. Of these eight, one showed clinical and laboratory evidence of dementia paralytica and the remaining seven were asymptomatic and revealed grade 2 to grade 3 cerebrospinal fluid reactions. Two cases of syphilitic aortitis with aortic insufficiency were discovered. A total of 18 patients had congenital syphilis. The remaining 117 patients had an early or latent stage of the disease.

During the original blood survey many of the group were found to have the primary and secondary stages of the disease, and whenever possible these patients were started on treatment (oxophenarsine hydrochloride [mapharsen®] and bismuth) immediately. A few of the group, however, had received more than 10 arsenical and 10 bismuth injections. Thus a total of 70 of the 145 patients had received some previous treatment.

Two treatment schedules were instituted. First, all patients were given a total of 240,000 units of penicillin G daily. The dosage was divided into four daylight doses of 30,000 units of aqueous penicillin given at three hour intervals. A nightly dose of 120,000 units was administered in a peanut oil suspension containing 2 per cent of white wax. The total penicillin dosage amounted to 2,400,000 units given in a 10 day period.

Secondly, 75 of the patients received, in addition to the pencillin, two injections per week of oxophenarsine hydrochloride in 0.04 Gm. doses and bismuth subsalicylate, 1 cc. given intramuscularly every five days. This group received in this manner a total of five arsenical and three bismuth injections. The members of this group were those patients who had received little or no treatment prior to their attendance at camp. No reactions of sufficient severity to warrant discontinuance of treatment were encountered.

The follow-up on this treated group has been extremely difficult. In the four years since treatment we have been able successfully to follow only 99 of the original 145 patients.

Results were as follows:

Early and Latent Syphilis.—Of 117 persons with early and latent syphilis 64 gave negative serologic reactions and were clinically well, 35 were not followed up, 12 had positive serologic reactions and 6 were deceased.

Central Nervous System Syphilis.—Of eight cases of syphilis of the central nervous system treated three were arrested, four were not followed up and one showed treatment failure.

The one case of dementia paralytica is included in the arrested group. However, the patient received an additional 9,000,000 units of penicillin to achieve this result. The one patient showing treatment failure went on to manifest a paretic formula although he remained asymptomatic.

Congenital Syphilis.—Of 18 cases of congenital syphilis, 11 were arrested, seven had no follow-up and 1 showed failure of treatment.

In the "arrested" group six patients attained a completely negative serologic reaction. The other five showed pronounced diminution in titer until at the time of writing they showed reactions up to 8 units by the Kahn quantitative method.

Cardiovascular Syphilis.—The two persons with cardiovascular syphilis had no follow-up.

All Cases.—Of the 99 patients who were followed up 84 per cent were serologically negative and 14 per cent remained serologically positive. It is interesting to note the rapidity and the extent to which this population became infected with syphilis—111 per 1,000. Only 5.5 per cent of the patients showed any evidence of central nervous system involvement.

329 Tegler Building.

ABSTRACT OF DISCUSSION

DR. JOHN E. RAUSCHKOLB, Cleveland: Canada, the largest of the countries of North America, has 3,500,000 square miles of territory and a population of 12,000,000 people. This represents a population of 3.3 per square mile. The 1931 census showed a population of approximately 130,000 Indians and Esquimos and 20,000 Negroes.

Alberta, one of the largest provinces of Canada, has an area of 250,000 square miles and a population of 800,000, the population density being 3.2 per square mile. Dr. Orr and his associates have done a very interesting piece of work under unusual and difficult circumstances.

Opinion is not yet unanimous as to the best treatment schedule, qualitative or quantitative, for the management of syphilis. Today some would administer 4,500,000 to 6,000,000 units of penicillin, or more, in divided dosage over a period of seven to 14 days. Various types of penicillin, too, have their proponents. Agreement has not yet been reached on the merit and true value of prepenicillin, concurrent or subsequent use of arsenical and bismuth therapy.

At Cleveland City Hospital since July 1, 1947, my associates and I have been studying the management of syphilis under two treatment schedules. One group has received 40,000 units of aqueous crystalline penicillin G intramuscularly every three hours for 60 doses, a total of 2,400,000 units as hospital treatment for 7½ days. The other group has received the same type and dosage of penicillin and, in addition, 0.4 Gm. (400 mg.) of oxophenarsine hydrochloride and 1.3 Gm. of bismuth subsalicylate in oil in 10 divided doses at weekly intervals. This program requires nine weeks. The first two doses of conjunctive therapy are given during the patient's hospital stay, and the other eight are given in the outpatient department.

The data of this study are as yet unpublished. The series is comprised of 136 patients. No case has been followed less than 10 months, and some have been followed for as long as 35 months. Of the 66 persons treated with the 2,400,000 units of penicillin alone, 16 have required re-treatment, an incidence of 24 per cent. Of the 70 patients treated with 2,400,000 units of penicillin plus 0.4 Gm. of oxophenarsine hydrochloride and 1.35 Gm. of bismuth subsalicylate only three have required re-treatment, a failure rate of 4 per cent.

In a paper, read at the annual meeting of this organization in 1947 and subsequently published, on the treatment of syphilis with 4,800,000 units of penicillin in oil and white wax administered in a course of eight days, a treatment failure rate of 31.03 per cent was reported.

Authoritative sources have estimated the incidence of syphilis in the United States at 1.3 to 2.4 per cent for the white population and 11.9 per cent for the Negro population. The geographic distribution of the disease bears a direct relationship to the distribution of the Negro population in the nation. A report on the incidence of syphilis among the Navajo Indians was given in 1937, based on hospital admissions at Sage Hospital, as 0.3 per cent in about 5,000 admissions.

Students of ethnologic and immunologic aspects of syphilis have stated there is no true racial resistance to the disease. Theories as to causes of racial variations in the incidence and severity of syphilitic infection are purely speculative. However, it has been generally accepted the white man, acquiring his syphilis from the Indian on the discovery of the New World and attenuating the severity of the disease over 200 years, introduced it to the African Negro in the commerce of slave trade. In the new host the disease regained the epidemiologic aspect of an exanthem. Such has been the course when the disease has been introduced to new hosts throughout the generations. Neurosyphilis is said to be relatively uncommon among Negroes, Chinese and Indians who have been more recent recipients of the infection.

I should like to ask Dr. Orr whether he ran his serologic tests concurrently. Furthermore, I should like to know whether there is any information available as to the amount of civilian influx in the area in the construction of the road, with some notion of getting an idea, perhaps, of the syphilis rate in the Indian. The paper was very interesting and, I think, timely.

Dr. Loren Shaffer, Detroit: I was interested in the figure on percentage of serologic reversal in these cases, which evidently represented a mixed group; I believe, Dr. Orr, that you said that about 86 per cent had reversal. That is an unusually high percentage, particularly if a fairly good percentage of the cases were of late syphilis. Since 86 per cent would be, as Dr. Rauschkolb has mentioned, an excellent percentage of reversal in early syphilis, it would possibly suggest that these cases represented largely new infections that had been brought into this racial group by outsiders under the influence of an expansion program and the building of the highway.

The other thing that I am sure we have all been very much interested in is the fact that since the war there has been a very decided drop in the incidence of new syphilis, particularly throughout the United States. For instance, in Detroit the total number of cases of primary and secondary syphilis reported in 1946 was approximately 2,000 cases. In 1947 it was 1,500 cases. In 1948 it was 1,000 cases. In 1949 it was 500 cases. In the Venereal Disease Clinic of the Detroit Health Department the number of cases of primary and secondary syphilis reported for the first three months of 1946 was 337. For the first three months of 1950 22 cases have been reported, a reduction of more than 90 per cent. Therefore, it becomes interesting and proper to take into consideration the tremendous drop in incidence of new syphilis in appraising the therapeutic effectiveness of treatment and control measures in this group.

A satisfactory explanation can hardly be made for this remarkable drop in the incidence of new syphilitic infections. The widespread use of penicillin in nonsyphilitic infections may be controlling the contagiousness of syphilis, if not actually curing the disease. Such use of penicillin should also be reducing the incidence of gonorrhea, and yet, unfortunately, in our Detroit experience at least, gonorrhea is nearly as prevalent as it was in 1946.

Dr. Paul A. O'Leary, Rochester, Minn.: In 1920 Dr. Harry Irvine established in the State of Minnesota the first statewide program for the reporting of venereal disease. Last year he surveyed the records and found there has been a steady drop in the incidence of syphilis in Minnesota since 1925. In other words, in that year there were some 4,400 cases of syphilis of all types reported, while in 1949 there were less than 400 cases reported, of which 69 were of acute syphilis.

I think the most outstanding observation was that in 1949, of the approximately 72,000 women who had serologic studies done while pregnant, only one had a child born with congenital syphilis. Perhaps some children born in 1949 will be found to have tardive congenital syphilis in the years to come. I don't believe that this drop in the incidence of syphilis is due to penicillin alone because a steady decline in the number of cases reported in the State of Minnesota has been going on since 1925, with two exacerbations. One was in the depression era of 1932, and the second, in 1946, when the war veterans returned.

Accordingly, penicillin should not receive all the credit for the reduction in the incidence of the disease, but acknowledgment also should be made of the accomplishments of the antisyphilis propaganda programs. The publicity and information thus released have also helped.

Dr. Hamnett A. Dixon, Toronto, Ontario, Canada: You may be interested in this observation: At the Toronto General Hospital all patients have routine blood Wassermann tests. Included are all persons admitted to the public wards, surgical or medical. In 1930 the percentage of positive reactions to Wassermann tests was 3.4. In 1949 the percentage of positive blood Wassermann reactions was 1.3.

Regarding the new patients admitted to the syphilis clinic at the Toronto General Hospital, in 1940 there were 345 new patients, with primary, secondary and tertiary stages of the disease. During 1949 there were 157 new patients, with primary, secondary and tertiary stages.

Dr. H. E. Michelson, Minneapolis: I am wondering what would have happened to these individuals had they not been treated for syphilis. I am reminded of the studies made on the Laplanders in the northern half of Norway and the studies made in Bosnia many years ago by the Austrians.

The people that Dr. Orr has dealt with have been exposed to the white man for many, many years, first to the fur trappers and later to the miners and other people who came into that country. Aside from the fact that some of these patients would have infected others there is no doubt that the condition would have simmered down to latency. I am of the opinion that, being the type of people they are, they would have been just about as well off if they had not been treated at all. It would be very interesting if, say, 20 years hence one would be able to investigate them again.

Dr. Everett S. Lain, Oklahoma City: I have been particularly interested in the historical records and the history of syphilis in the American Indians, especially as regards the recent decrease of syphilis. Dr. Michelson also touched on the increase since the Indian became intermixed with the "paleface."

Some years ago I began to read about the origin of syphilis, when the historians conjectured that perhaps syphilis among the whites was contracted from the Indians. I never could subscribe to this opinion. It was my privilege between 1902 to 1915 to visit and personally examine several thousand full-blooded aborigines in Oklahoma and New Mexico. In that territory, where the population numbered 40,000 to 50,000, I was strikingly impressed with the rarity of syphilis.

But I did see many cases of various types of leukodermatosis and lupus that might have given origin to the speculation by the early historians that these conditions were syphilis and that the white man acquired the disease from the Indian. During my early examinations I did not routinely make Wassermann tests. That work was begun even before the development of the Wassermann test. But later I did, and I was surprised to find that the incidence of positive Wassermann reactions ran less than 0.75 per cent.

Now, the situation is quite different among the few Indians who drift into our public clinics. I am personally confident that the Indian probably acquired syphilis after he became intermixed with the whites, but more especially after contact with Negroes, with whom Indians are frequently intermarried. I cannot believe that syphilis was a disease originally common to the American Indian.

Dr. Norman N. Epstein, San Francisco: I think you might be interested in the statistics from the United States Marine Hospital in San Francisco, where the cases of venereal disease come, to a large extent, from outside the country. It is well known that there has been a pronounced drop in incidence of acute syphilis in the United States. It seems as though the same is true in the Orient. In the admissions for 1946 there were 159 cases of primary syphilis and 40 of the secondary type. In 1947 there were 166 cases of primary syphilis and 55 of

secondary syphilis. We haven't the figures for 1948. In 1949 there were 88 cases of primary syphilis and 12 of secondary, approximately half the number for 1946. In the first three months of this year there have been 18 cases of primary syphilis and two of secondary.

DR. LOUIS CHARGIN, New York: I, too, was struck by the unusually good results obtained by Dr. Orr in his cases. Perhaps the "measuring rod"—i. e., the serologic test employed—was undersensitive. In New York we have also observed a drop in the number of new infections reported. It is not easily explained.

DR. HAROLD ORR, Edmonton, Alberta, Canada: I should like to thank Dr. Rauschkolb and the others who participated in the discussion. In Alberta all blood samples submitted are screened by a sensitive Kahn test. Those that give positive reactions are then tested by a standard quantitative Kahn test and by the Kolmer modification of the Wassermann test.

We attribute the rather high cure rate to the following factors:

1. The syphilis was new. The epidemic began with the arrival of Negro labor troops from the southern part of the United States. Many of these Negroes were transported in trucks from Edmonton to the highway at Dawson Creek. Night bivouacs en route facilitated the spread of the disease.

2. The treatment was thorough for 1946, consisting in most cases of 10 intravenous injections of oxophenarsine hydrochloride and administration of a considerable amount of a bismuth preparation with and following the course of 2,400,000 units of penicillin.

3. It was impossible to run down the significance of all the positive serological reactions, and undoubtedly some of the persons treated were not syphilitic.

The purpose in presenting this paper is to inform you of what is being done to control this disease in the territory contiguous to the Alaska Highway, the hinterland of this continent.

EFFECTIVENESS OF PENICILLIN IN THE PREVENTION OF CONGENITAL SYPHILIS

LOREN W. SHAFFER, M.D.
AND
CHARLES J. COURVILLE, M.D.
DETROIT

A TOTAL of 631 pregnant women delivered during 1948 and 1949 were treated with penicillin either before or during pregnancy at the Social Hygiene Clinic of the Detroit Department of Health. Various schedules of treatment were used. Most patients received ambulatory treatment with repository penicillin in total doses of 3,600,000, 4,800,000 or 9,600,000 units. Some were given aqueous penicillin G totaling 2,400,000 or 4,800,000 units, and another group received 3,000,000 units of repository penicillin with or without oxophenarsine hydrochloride and a bismuth preparation during 10 days of hospitalization. No appreciable difference in the effectiveness of these schedules was noted, and no separate analysis according to the schedule employed will therefore be made. Data on every pregnant woman who was treated with penicillin in the clinic and delivered during this two year period are included.

The majority of these women were delivered at the Herman Kiefer Hospital operated by the Detroit Department of Health. Information on serologic tests of the mothers, cord bloods, roentgenograms, status of placenta and of the baby at birth was readily available from that institution. Our information on patients delivered at private hospitals or in homes is much less complete. In nearly all instances the follow-up examinations on the babies were done at the Social Hygiene Clinic.

Not all these women received penicillin treatment during their pregnancies. Some who had apparently responded satisfactorily to previous treatment were intentionally allowed to go through pregnancy untreated. We ordinarily did not re-treat women who had previously received adequate penicillin therapy according to the above-mentioned schedules, who were clinically normal and who had demonstrated a decline in serologic titer to negative. Likewise, if treatment was recent, no additional penicillin was given if the titer was decreasing in a satisfactory manner. Many patients, particularly those with late syphilis with titers of 1 to 8 Kahn units, were carried throughout pregnancy without additional treatment. Others would have been treated but for various reasons were uncooperative and were infrequently seen at the clinic.

Table 1 indicates the division of cases in the group according to the time of treatment in relation to pregnancy.

Read at the Seventieth Annual Meeting of the American Dermatological Association, Inc., Jasper National Park, Alberta, Canada, June 20, 1950.

These 631 pregnancies resulted in 636 infants, there being five sets of twins in the group. There were 58 disastrous results in these pregnancies. The results of these pregnancies are listed in table 2.

In analyzing the effect of syphilis on pregnancy it is difficult to determine whether or not the infection actually was the cause of the disastrous termination of the pregnancy. In any group of nonsyphilitic women there will be a definite incidence of unfortunate terminations of the pregnancies. Reports of the incidence of abortions, stillbirths and neonatal deaths vary quite widely with the type of patient and the reporter. This point holds especially true for abortions or mis-

TABLE 1.—*Classification of Patients According to Time of Treatment in Relation to Pregnancy*

Treated prior to pregnancy only		225
Treated during pregnancy only		191
First trimester	32	
Second trimester	54	
Third trimester	105	
Treated both prior to and during pregnancy		215
Total		631

TABLE 2.—*Results of Pregnancies*

Abortions and miscarriages	16 (2.51%)
Stillbirths	21 (3.3%)
Neonatal deaths	16 (2.51%)
Living syphilitic children	5 (0.8%)
Lost	3 (0.47%)
Normal babies	575 (90.41%)
Total	636

TABLE 3.—*Prognosis in Pregnancy of Syphilitic and Nonsyphilitic Women*

	Nonsyphilitic (University of Pennsylvania [1]), Per Cent	Syphilitic (Detroit), Per Cent
Miscarriages and abortions	5.70	2.51
Stillbirths and prematurity	3.70	3.30
Neonatal deaths	3.00	2.51
Normal full term infants	87.60	90.41

carriages. Better and more accurate reporting of stillbirths and neonatal deaths has helped to standardize these figures.

The disastrous results of these pregnancies of syphilitic women compare very favorably with general figures given for the prognosis of pregnancy. The disastrous results reported by Ingraham, Rose and Beerman [1] from the Philadelphia General Hospital in 4,902 nonsyphilitic pregnancies are compared with those in our series in table 3.

1. Ingraham, N. R.; Rose, E. K., and Beerman, H.: Treatment of the Syphilitic Pregnant Woman with Penicillin in Absorption-Delaying Vehicles, in A Symposium on the Current Progress in the Study of Venereal Diseases, United States Public Health Service, Division of Venereal Disease, April 7 and 8, 1949, Washington, Government Printing Office, 1949, pp. 34-39.

The stillbirth rate for the City of Detroit for the years 1946 through 1949 averaged 2.13 per cent.

In attempting to determine whether or not abortions, stillbirths and neonatal deaths were due to syphilis we tried to correlate all the available data. We held the major premise, although realizing that exceptions can occur, that a woman adequately treated for syphilis who shows satisfactory response to therapy over a period both during and after pregnancy will deliver a normal child. We felt that an abortion was not due to syphilis if the mother was seronegative and maintained seronegativity. Likewise, one who after considerable therapy was serologically fast at a low titer during and after pregnancy would not infect the fetus. Autopsies were permitted in a number of cases of stillbirth and neonatal death. We did not feel that a positive reaction of the cord blood alone was diagnostic of an infected fetus if other observations indicated that this reaction represented merely a passive transfer of reagin from a serologically positive mother in whom the condition was well controlled. We have attempted by careful analysis of all the available information in each case to judge whether or not each disastrous result of pregnancy was probably due to syphilis, possibly due to syphilis or probably not due to syphilis. Table 4 indicates our impressions in this regard.

TABLE 4.—*Causes of Disastrous Results of Pregnancies*

Probable Classification	Abortion	Stillbirth	Neonatal Death	Infected Child	Total	Per Cent
Due to syphilis	0	1	1	5	7	1.1
Possibly due to syphilis	5	5	4	0	14	2.2
Not due to syphilis	11	15	11	0	37	5.8
Total	16	21	16	5	58	9.1

Abortions.—None of the 16 instances of abortion were thought to be definitely due to syphilis. Three mothers were seronegative and remained so; nine mothers had titers of 4 Kahn units or less and their quantitative serologic reactions remained at that level or declined after abortion. Two mothers with early latent syphilis were seropositive with a titer of 16 Kahn units and remained asymptomatic but serologically fast for several months after delivery. One mother was treated for secondary syphilis during the second trimester. She was seropositive with a titer of 64 Kahn units at that time. She miscarried at 6 months (one month after treatment) but was seronegative six weeks later. We felt that syphilis was definitely not a factor in 11 of these cases but could possibly have been a factor in five instances.

Stillbirths.—There were 21 stillbirths in the group; in 15 instances we felt that syphilis was definitely not the cause of the fetal death. The mothers in 10 of these cases were seronegative during pregnancy and at delivery, and there was no evidence of relapse after delivery. The mothers of five more stillborn infants had received considerable treatment, and, although they remained seropositive, clinical and serologic evidence at the time of delivery did not suggest that syphilis was the cause of the fetal death. Prematurity, asphyxia from prolapsed cord and birth injuries were given as the causes of these deaths. There were five stillbirths from mothers who had been adequately treated but were still seropositive without evidence of relapse. There were not sufficient data on the cause of these still-

births to rule out syphilis without question. They were classified as possibly due to syphilis. In one instance a pregnant woman was treated for early latent syphilis during the eighth month of pregnancy with 600,000 units of penicillin in oil and wax daily for 10 days while in the hospital. She noted abdominal pain during therapy and delivered a stillborn child one week later at home. Unfortunately, there is no definite information available on the child. It is possible that this case is an example of placental therapeutic shock resulting in fetal death. There were two other similar cases in our group classified as possibly related to syphilis, in which one or two injections of penicillin had been given shortly before the stillbirth occurred. Bowen and co-workers,[2] Ingraham and Beerman [3] and Hyman and McCain [4] have described similar cases. The Herxheimer reaction may result occasionally in fetal death. Further study of this reaction in relation to pregnancy and a practical means for its prevention are needed.

Neonatal and Infant Deaths.—Sixteen infants died within a few weeks after delivery. One mother who had been treated one year prior to pregnancy for secondary syphilis was seronegative at the sixth month of pregnancy. She was not seen again until the time of delivery, when the reaction to the serologic test for syphilis and the cord blood Kahn reaction were positive. The infant died on the fifth day, and autopsy revealed cerebral edema and enteritis. The pathologist diagnosed congenital syphilis.

In the remaining 15 cases the cause of death was stated to be as follows:

Prematurity	4
Pneumonia	3
Diarrhea	2
Congenital Defects	2
Birth Injury	1
Suffocation	1
Auto accident	1
Cause unknown (mother's serologic reaction and cord serologic reaction negative)	1

Careful consideration of the data available on these cases indicated that syphilis was not a factor in 11 of the above-mentioned 15 cases, but there were insufficient data to rule out the possibility of syphilis being a factor in four cases.

Congenitally Infected Infants.—There were five living infants for whom a diagnosis of congenital syphilis was made and treatment instituted. In four of these cases the mothers had received adequate therapy and had shown early satisfactory serologic response. However, these four women were lost from observation during the latter part of pregnancy and during this time they either had relapses or were reinfected. The mother in the fifth case showed seroresistance to exten-

2. Bowen, J. H.; Cole, H. N.; Driver, J. R.; Light, R. C., and Rauschkolb, S. C.: Herxheimer Reactions in the Penicillin Treatment of Syphilis in Pregnancy, Arch. Dermat. & Syph. **58**:735 (Dec.) 1948.

3. Ingraham, N. R., and Beerman, H.: The Present Status of Penicillin in the Treatment of Syphilis in Pregnancy and Infantile Congenital Syphilis, Am. J. M. Sc. **219**:433 (April) 1950.

4. Hyman, A., and McCain, J.: Syphilis in Pregnancy, New England J. Med. **241**: 960 (Dec. 15) 1949.

sive therapy. The baby was found to be seropositive, with a quantitative titer of 32 Kahn units at 1 month, without clinical signs of syphilis, and was treated on this basis. The infant was seropositive with a titer of 8 Kahn units at 10 weeks, and seronegative at 4½ months. Although included here as having congenital syphilis, this baby quite possibly might have progressed to seronegativity without treatment. There were two infants given penicillin therapy at other hospitals before the age of 2 months. The diagnosis of congenital syphilis was not made on either child, and all the evidence available indicated that they were not infected. They were considered as normal infants in our analysis.

The histories of the congenitally infected infants are briefly summarized as follows:

CASE 1 (151035-316164 [W. T.]).—Congenital syphilis.

The mother was diagnosed as having secondary syphilis in August 1948. Her reaction to the serologic test for syphilis was positive, with 256 Kahn units, and the result of dark field examination was positive. She was given 9,600,000 units of procaine penicillin in oil from Aug. 25 to Oct. 18, 1948. Her serologic reaction became negative on May 3, 1949, and was still negative on June 17. She was delivered of a full term male child on July 17. At delivery her serologic reaction was positive. The cord blood reaction was negative. One month later, on August 16, when the mother was again seen in this clinic, her serologic reaction was positive, with 128 Kahn units, and she was subsequently found to have genital syphilides. She was diagnosed as having recurrent secondary syphilis and re-treated, although she probably had been reinfected from her husband. Examination of the baby on August 16 revealed normal clinical observations and a negative serologic reaction. On September 13 the baby's serologic reaction was positive. On September 20 there was a generalized papulosquamous eruption, and the Kahn test gave a positive reaction, with 128 Kahn units. A diagnosis of early congenital syphilis was made, and the baby was treated. The mother had a relapse or was reinfected during the last month of pregnancy. The baby was infected very late in pregnancy. The disease was evidently in the incubation period at birth, and there was no clinical or serologic evidence of infection until eight weeks after birth.

CASE 2 (307029 [N. C.]).—Congenital syphilis.

The mother was first seen by us on June 28, 1948, with dark field-positive lesions and a positive quantitative Kahn reaction in a dilution of 1:16, or 64 Kahn units. Her condition was diagnosed as secondary syphilis. She was treated in June 1948 with 4,800,000 units of penicillin G in oil and wax. Her serologic titer declined to 1:1 in February 1949, at which time she was found to be five months pregnant. She was lost from observation during the remainder of her pregnancy. She was delivered at her home on June 24, 1949. She was examined by us on September 13, at which time her serologic reaction was positive, with 64 Kahn units, and she was re-treated as having a serorelapse. The baby was found to have a positive serologic reaction and lesions positive on dark field examination at Children's Hospital in August 1949. The quantitative serologic titer varied between 1:50 and 1:100. A diagnosis of congenital syphilis was made, and the baby was treated. The mother had a relapse during the latter part of pregnancy while lost from observation.

CASE 3 (295386-313133 [M. O.]).—Congenital syphilis.

The mother was found to have secondary syphilis, with a serologic reaction positive in a 1:64 dilution, and was five months pregnant on Nov. 18, 1948. She was given 3,000,000 units of penicillin at Herman Kiefer Hospital from Nov. 23 to Dec. 2, 1948. Her serologic titer declined to 1:1 on Jan. 6, 1949, but rose to 1:16 on February 9. After this last date she was lost from observation until delivery on March 8, when she was reported seronegative. At the time of her next examination, on April 8, she was found to have recurrent secondary syphilides and a positive serologic reaction in a 1:32 dilution. She also had asymptomatic neurosyphilis as evidenced by a positive reaction of the cerebrospinal fluid.

A male baby was born in good condition on March 8, 1949. The cord Kahn reaction was positive, and roentgenologic examination of the long bones revealed normal conditions. The

reaction to a serologic test on the baby was positive with a titer of 1:32, at 1 month, and the baby had a skin eruption and rhinitis characteristic of congenital syphilis. He was placed under treatment.

The mother had a relapse during the latter part of pregnancy and was lost from observation. The report of a negative serologic reaction at the time of delivery is thought to have been due to a laboratory error.

CASE 4 (298722 [M. J.]).—Congenital syphilis.

The mother was treated for secondary syphilis in July 1947, with 200 mg. of oxophenarsine hydrochloride, 600 mg. of a bismuth preparation and 3,000,000 units of penicillin in oil and wax in 10 days. She was seronegative from December 1947 to April 1948. A single serologic reaction was reported positive in May 1948, but the patient could not be located for a recheck serologic test or treatment. At delivery, on June 16, 1948, the mother's serologic reaction was positive, with 128 Kahn units, the cord Kahn reaction was positive and roentgenologic examination of the baby's long bones revealed no abnormality. The serologic test for syphilis on the baby's blood gave a negative reaction in one month. At 4 months of age, when next examined, the baby had rhinitis, a skin eruption, enlarged liver and spleen and roentgenologic evidence of periostitis in the long bones. The serologic test gave a positive reaction, with 40 Kahn units, and observations on the cerebrospinal fluid were normal. A diagnosis of early congenital syphilis was made, and the baby was treated with penicillin. The mother was re-treated as evidencing a probable treatment failure.

This case is interesting in that the baby was evidently infected late in pregnancy and the disease was in the incubation period at the time of delivery. The positive cord Kahn reaction, indicating that it represented a transfer of reagin from the mother reversed to negative, but the child later manifested typical congenital syphilis.

CASE 5 (309876-317876).—Probable congenital syphilis.

The mother was first seen in October 1948, at which time she was five months pregnant and the serologic reaction was positive in a 1:128 dilution. Her condition was diagnosed as late latent syphilis, and she was treated with 600,000 units of procaine penicillin twice weekly for eight weeks (9,600,000 units) from Nov. 5 to Dec. 24, 1948. There was wide fluctuation in her serologic titer, which varied from 1:4 to 1:256 without any pattern. The titer two weeks before delivery was 1:64. The patient was delivered on Feb. 24, 1949. One month later her serologic titer was still 1:64 and she was re-treated with procaine penicillin in oil, a bismuth preparation and oxophenarsine hydrochloride. She finally became seronegative in March 1950, after her third course of penicillin.

The infant's cord blood Kahn reaction was positive at delivery, and roentgenologic examination of the long bones revealed no abnormality. On March 22, 1949, the baby's serologic reaction was positive in a 1:8 dilution. There were no clinical manifestations but a diagnosis of congenital syphilis was made and treatment instituted. On May 6, 1949 (at age 2½ months), the baby had positive serologic reaction in a 1:2 dilution. However, on the next examination, on May 7, she was seronegative and remained so.

The mother was well treated during the latter part of pregnancy, but the serologic reaction remained positive, with a high titer. The baby was treated on the basis of a positive serologic reaction (1:8 dilution) at the end of one month, and the serologic reaction became negative at 4½ months. The case might have progressed to seronegativity without treatment and is therefore classified only as probable congenital syphilis.

TREATMENT WITHHELD DURING PREGNANCY

There were 225 women previously treated with penicillin alone or in combination with oxophenarsine hydrochloride and a bismuth preparation who were allowed to go untreated during their pregnancies. Treatment had been given a few months to four years prior to conception. The therapy was intentionally withheld in most of these cases because the previous treatment was considered adequate. The patients were clinically normal and either seronegative or seropositive with a low titer. They were expected to return to the clinic at monthly intervals for clinical and serologic check-up. Not all patients were cooperative in this

respect. Some pregnant women did not return for the recommended treatment during pregnancy. Relapses were missed in a few cases because the women failed to return for monthly examinations in the clinic. As a result, some patients who would otherwise have been re-treated either for relapse or prophylactically did not receive therapy.

Table 5 indicates the outcome of pregnancy when therapy was not given during pregnancy. A comparison is made between persons who were seronegative or not serologically tested and those who were seropositive at delivery. The group that did not have serologic tests at delivery had been seronegative during pregnancy.

There were 10 disasters terminating pregnancy in women in the first group. In each instance the mother had been seronegative during pregnancy and at term or shortly after delivery. None of these unfortunate results was considered to be due to syphilis.

Among the 14 disasters in the group of seropositive mothers, three were due to relapse late in pregnancy which was not discovered until delivery or later.

TABLE 5.—*Outcome of Pregnancy When Mother Was Not Re-Treated During Pregnancy*

Serologic Reaction of Mother at Delivery		Reaction of Cord Blood		No. of Patients Lost from Observation	No. of Normal Living Babies	No. of Disasters		
Negative...	134	Negative...	102			Abortions.....	3	
		Positive...	0			Stillbirths.....	4	
Not taken.	33	Not taken.	65	2 (1.2%)	155 (92.8%)	Neonatal deaths	1	
						Syphilitic child..	0	
	167							10 (6.0%)
Positive...	58	Negative...	22			Abortions.....	5	
		Positive...	8			Stillbirths.....	5	
		Not taken.	28	1 (1.7%)	43 (74.2%)	Neonatal deaths	2	
						Syphilitic child..	2	
								14 (24.1%)

The mothers had shown satisfactory response to previous therapy in the early months of pregnancy but did not cooperate for monthly observation as recommended. In three other instances therapy had been recommended but the patients did not cooperate. Another patient falsely alleged that she was being treated by a private physician. Of the remaining seven cases, three were classified as probably not due to syphilis and four were thought possibly a result of syphilis on the basis of the available evidence. In none of these seven cases was there definite evidence of fetal death as a result of syphilis.

These figures indicate that pregnant women who have been treated previously for syphilis need not be re-treated if they have progressed to seronegativity and remain there. Likewise, seroresistant cases, particularly of late syphilis with a positive serologic reaction, with low titer, need not be re-treated. However, this small series suggests that it is advisable to re-treat a pregnant woman when there is any question of unsatisfactory response to previous therapy or of her willingness to remain under close observation.

RESULTS OF TREATMENT OF PREGNANT WOMEN WITH INFECTIOUS SYPHILIS

There were 27 women treated for early primary and secondary syphilis during pregnancy. All received between 3,000,000 and 9,600,000 units of repository

penicillin. Thirteen received an additional five injections of oxophenarsine hydrochloride (mapharsen®) and three injections of a bismuth preparation. The results are summarized in table 6.

The abortion occurred at 6 months, at which time the mother was seronegative. One baby died on the first day of prematurity and respiratory failure without evidence of syphilis. It weighed 2 pounds (907 Gm.). The mother became seronegative without further therapy. The other two babies were seronegative at 1 month. One died in an automobile accident and the other of pneumonia.

The two instances of syphilitic infants are cases 1 (151035-316164 [W. T.]) and 3 (295386-313133 [M. O.]), which are abstracted above. In both there was evidence of treatment failure or reinfection during the last month of pregnancy which was not detected in time to re-treat the mother prior to delivery. These cases demonstrate the need of close follow-up of the mother throughout pregnancy. Tucker [5] has reported on a group of 149 pregnant women with early syphilis who were treated with penicillin with no disasters due to syphilis.

TABLE 6.—*Results of Treatment in Pregnancy Complicated by Primary and Secondary Syphilis*

Time of Treatment			
First trimester	6		
Second trimester	11		
Third trimester	10		
Outcome of Pregnancy			
Normal child	21		
Abnormality	6		
		Not Due to Syphilis	**Due to Syphilis**
Abortion		1	0
Neonatal death		3	0
Congenital syphilis		0	2

SIGNIFICANCE OF POSITIVE SEROLOGIC REACTION OF CORD BLOOD

Kahn tests were done on the mother's blood and the cord blood in 395 deliveries in Herman Kiefer Hospital. The mother's serologic reaction was found to be positive to some degree in 227 instances and negative in 168 cases. The cord blood reaction was positive or doubtful in 100 cases and negative in 294 cases. There was hemolysis in one cord blood specimen. There were only two instances of the reaction of the cord blood's being positive when that of the mother's blood was reported negative. In both instances the mother's blood reaction was strongly positive within one month after delivery. In these cases it was thought that there had been an error in the tests of the mothers' bloods rather than false positive reactions of the cord bloods. Table 7 indicates the ultimate observations on babies born with positive cord blood reactions.

All babies born of syphilitic women were scheduled to be examined in the clinic at four week intervals for four to 12 months. Quantitative Kahn reactions were taken at these times. Progressive decline in quantitative titer was interpreted as indicating that the outcome would probably be satisfactory. The mothers were examined also for evidence of clinical or serologic relapse. Of the 100 babies born with positive cord blood reactions 92 progressed to seronegativity without treatment. Two were lost from observation. Two died from causes not related to syphilis. Four of the group were found to have congenital syphilis. The diagnostic signifi-

cance of positive cord blood reactions would, of course, be much greater in untreated mothers, but it is surprising that only 4 per cent of the babies in this group with positive cord blood Kahn reactions proved to have congenital syphilis as determined by further follow-up.

There was one baby born with a negative cord blood reaction of a mother who had had a relapse during the last month of pregnancy. The reaction to the serologic test for syphilis on the baby's venous blood was negative at one month but positive at the second month and associated with cutaneous lesions of congenital syphilis. The baby was evidently born during the incubation period of the syphilis.

These observations indicate that a positive reaction to a serologic test for syphilis on cord blood is not of itself diagnostic of syphilis in the infant, and this is especially true if the mother has received treatment. Careful observation of the mother and child with frequent quantitative serologic tests for syphilis on the infant should be made to determine the diagnosis and need for therapy; dropping

TABLE 7.—*Ultimate Observations on Babies Born with Positive Cord Blood Reactions*

Achievement of Seronegativity (Total, 92)	
Seronegative in one month	61
Seronegative in two months	21
Seronegative in three months	4
Seronegative in four months	1
Seronegative in five months	2
Lost from observation for one year, then seronegative	3
Miscellaneous	
Lost from observation	2
Died from causes not related to syphilis	2
Died from congenital syphilis	1
Living syphilitic infants	3
Grand total	100

quantitative titers call for further observation; persistent or rising titers at fairly high levels justify diagnosis and treatment, and, conversely, a negative cord blood reaction is not conclusive proof that the child is not infected.

It is also believed that in those cases in which the serologic reaction remained positive for more than 2 months the babies were probably infected in utero but responded in a satisfac[illegible]nner both clinically and serologically to the treatment administered to the mo[illegible]er. Tucker [5] also noted persistence of reagin in babies whose mothers were treated late in pregnancy. It is never, therefore, too late to treat the mother in the hopes of curing an infected fetus in utero. It is suggested that a massive dose (2,400,000 units of "96 hour" procaine penicillin) could well be administered at term or even early in labor with good results. Hyman and McCain [6] cite an instance of an infected fetus being cured by penicillin given the mother during the last week of pregnancy.

Weiner [7] has shown that two antibodies are produced in the Rh-sensitized mother: the bivalent antibody, which is retained in the intact placenta, and the

5. Tucker, H.: Penicillin Therapy Administered During Pregnancy, Am. J. M. Sc. **217**: 157 (Feb.) 1949.

6. Footnote deleted.

7. Weiner, A. S.: Rh Factor in Immunological Reactions, Ann. Allergy **6**:293 (May-June) 1948.

univalent antibody, which passes through the intact placenta and has the capacity to fix complement. Rein and Kostant [8] stated:

> In the comparison of titers of reagin antibody in adequately treated syphilitic mothers and in their normal fetuses, it has been observed that a similar separation of univalent and bivalent antibodies seems to be effected. In the complement fixation tests for syphilis (detecting univalent antibodies) similar titers of reagin are found in the mother and in the fetus. In the flocculation test (detecting bivalent antibodies) the level of reagin antibody titers in the infant is minimal as compared with that of the mother.
>
> Thus it is apparent that two varieties of antibodies, the univalent and the bivalent, may be produced in syphilitic infection. In syphilotoxemia (the passive transfer of reagin antibody to nonsyphilitic offspring of syphilitic mothers), the univalent antibodies predominate. In true prenatal syphilis both varieties of antibodies may be found in similar amounts . . . the univalent complement-fixing antibody . . . readily passes the intact placenta.

Complement fixation tests on cord or venous blood of the infant parallel the titer of the mother's blood and would have little diagnostic significance in the infant. The bivalent flocculation antibody does not readily pass the intact placenta and is of more diagnostic value on the cord or venous blood of the infant. Our experience confirms Dr. Rein's observation that the titer of cord Kahn reactions is consistently lower than that of the mother's blood reaction in the absence of infection in the infant. Treatment of the infant, however, may not be called for in spite of a strongly positive flocculation test alone if the mother was adequately treated late in pregnancy, since this treatment should also prove adequate for the fetus.

ROENTGENOGRAMS OF THE LONG BONES

Roentgenograms of the long bones were taken within the first week on nearly all babies born with positive reactions to serologic tests of the cord blood. In five instances in which the mother received penicillin therapy late in pregnancy, roentgenologic observations were present that were considered diagnostic of osseous syphilis. These babies were observed to attain seronegativity without treatment.

An additional baby having a positive cord blood Kahn reaction at birth had negative roentgenologic findings at 1 week of age. The baby's serologic reaction was reported as reversing to negative at 1 month. The baby was not seen again until 4 months of age, at which time the serologic reaction was again positive and the baby had active congenital syphilis consisting of a cutaneous eruption, rhinitis, enlarged liver and spleen and roentgenologic changes in the long bones typical of syphilis. The mother had had a relapse late in pregnancy but had not been re-treated. The disease in the infant was evidently in the incubation period at the time of the baby's birth.

Roentgenologically observed changes in the long bones indicate that the baby has acquired syphilis in utero, but if the mother receives adequate treatment even after these changes develop there is an excellent chance that the treatment administered to the mother will also cure the baby. In other words, roentgenologically observed changes in the long bones discovered at birth do not of themselves call for further treatment of the baby provided the mother received adequate treatment late in pregnancy.

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8. Rein, C. R., and Kostant, G. H.: Nature of Antigens and Antibodies in Serology of Syphilis, Arch. Dermat. & Syph. **60**:217 (Aug.) 1949.

SUMMARY AND CONCLUSIONS

This report is a study of the incidence of congenital syphilis in the offspring of 631 syphilitic pregnant women treated with penicillin and delivered during 1948 and 1949. The incidence of abortions, miscarriages, stillbirths and neonatal deaths closely parallels that reported for nonsyphilitic pregnancies.

We classify as syphilitic five infants, one stillbirth and one neonatal death, or 1.1 per cent. It was believed that placental shock may have been the cause of the one stillbirth classified as syphilitic. The neonatal death and the presence of congenital syphilis in four of the infants were due to relapse or reinfection late in pregnancy in women who failed to remain under observation. The remaining infant diagnosed as syphilitic was treated at 1 month on the basis of a positive serologic reaction and may not have had syphilis.

Women who have been adequately treated and have progressed to seronegativity do not need to be re-treated during pregnancy, provided the serologic reaction remains continuously negative. Likewise, those with seroresistant cases, particularly of seropositive late syphilis with low titer, need not be re-treated. However, the increase in disastrous results that occurred in the seropositive cases in this series suggests that it is advisable to re-treat the pregnant woman when there is any question of unsatisfactory response to previous therapy or of her willingness to remain under close observation.

Positive reactions to serologic tests on cord blood are not diagnostic of congenital syphilis, especially in well treated mothers. The reaction to the Kahn test on the cord blood was positive in 100 infants from 227 mothers whose serologic reactions were positive at delivery. Only four cases of congenital syphilis were diagnosed in these 100 infants. The presence of univalent and bivalent antibodies in fetal blood as described by Rein is reviewed.

The babies of mothers treated late in pregnancy may show persistent but gradually decreasing titers that may require several months to become negative. These probably represent infants infected in utero but responding in a satisfactory manner to the treatment administered to the mother. Likewise, osteitis of the long bones as demonstrated by roentgenograms in such infants does not necessarily call for further treatment.

Penicillin therapy should be given at any time in pregnancy short of actual delivery. If it is too late to prevent infection, such treatment is very effective in "curing" the condition of an infected fetus in utero.

Adequate penicillin treatment given during pregnancy is nearly 100 per cent effective in the prevention of congenital syphilis or in curing an already infected fetus in utero, provided further serologic and clinical progress is satisfactory.

ABSTRACT OF DISCUSSION

DR. UDO J. WILE, Ann Arbor, Mich.: Dr. Shaffer's and Dr. Courville's interesting paper is an excellent review of the effectiveness of treatment in limiting the occurrence of congenital syphilis. The very large percentage of success of the various treatment programs employed in a large series of cases presents perhaps the most encouraging picture in the therapy of syphilitic infection. In this group of cases not only were the mothers themselves evidently cured but also, even when their infection was still evidenced by a positive serologic response, energetic treatment in practically any stage of the pregnancy gave a very high percentage of assurance that the product of conception would be uninfected.

At first glance table 2 would seem to indicate that an appreciable percentage of the children had actually been infected in utero despite treatment. Sixteen cases of miscarriage and abortion and 21 stillbirths lose their significance when compared with the fetal mortality figures of pregnancies not complicated by syphilitic infection. Actually, in this large series of cases, in only 0.8 per cent did the pregnancies result in living syphilitic children. The authors have emphasized the now well known dictum that the examination of the cord blood is of little or no value in establishing the syphilitic status of the child.

Where the cord blood reaction is positive, in the vast majority of cases that observation merely indicates a transfer of the mother's reagin to the child. Of greatest interest, I think, is the analysis of what occurs when treatment is withheld during pregnancy in patients previously treated with penicillin or with penicillin in combination with oxophenarsine hydrochloride and a bismuth preparation. In this large series there were no more abortions or stillbirths than would have occurred in a similar group of nonsyphilitic women. Only two cases of syphilitic infants occurred in this group, in which 58 mothers had positive serologic reactions during their pregnancy.

Under ordinary circumstances persons in this last group would surely have been treated on the basis of their positive reactions and the two treatment failures in the infants could have been avoided. Dr. Shaffer and Dr. Courville have not mentioned in their paper a situation which has troubled the statistical division in the Public Health Service: There is a very decided drop in the incidence of syphilis in practically all its stages in this country, particularly since the introduction of antibiotic therapy. Paradoxically, there seems to be a considerable increase in the number of reported cases of congenital syphilis.

I do not believe that is a true paradox. To begin with, far more children are being examined on the basis of their parents' positivity as a result of the increased public interest in the whole syphilis problem. Institutions which never reported them before are reporting congenital syphilis cases. Many of these, indeed, occur in older individuals whose infection dates back to their parents over several decades. Not included also are innumerable cases observed in health surveys and in the newly adopted screening tests for tuberculosis and other infectious diseases. It would seem beyond any peradventure that if syphilis is being controlled in its acquired form and cured there must be an actual decrease in the instance of the congenital pattern.

This paper which has just been presented is the result of a very painstaking investigation. To have followed so large a number of cases with such a relatively low case loss is a real achievement, and Dr. Shaffer and Dr. Courville are to be congratulated not only on the success of their investigation but also on their excellent follow-up.

I should like to put one qualification into the conclusion which could be drawn from this paper. These results really parallel those which were accomplished years ago with continuous treatment with arsenic and bismuth preparations during the period of gestation, and there was no form of syphilis therapy in which more gratifying results were achieved when two or three individuals could be treated with a single dose, so to speak. There is a real reason for that: Pregnant women are very easily induced to carry on the treatment. There is a low case loss in that group. I think beyond any doubt that excellent results were achieved before the period of present therapy.

Where I should most like to qualify the conclusions, however, is with regard to the type of case. I find it difficult to believe that a woman who is infected during her pregnancy in the early stages and who carries the child almost to term and then receives treatment can produce an infant wholly free from the infection. To be sure, the child may have no obvious manifestation, and it may well be that the serologic reaction is negative and remains so, but to determine that that child is free from the structural changes of syphilis, syphilis of the liver, syphilis of the heart and syphilis of the type which manifests itself by major and minor deviations from the normal, must involve a survey over a period of years. How many of these children might acquire the disease I don't know. Except for that qualification I think this paper is entirely sound, and I think the authors ought to be congratulated on the excellent results.

DR. STEPHEN ROTHMAN, Chicago: Old type treatment methods were entirely sufficient to prevent prenatal syphilis if treatment was started early in the course of pregnancy. However,

penicillin seems to have the great advantage that it might be effective in relatively very late stages. Also, the fact that penicillin is nontoxic for all practical purposes represents a tremendous advantage.

DR. LOUIS CHARGIN, New York: I want to join Dr. Wile in congratulating the presenter of the paper; it is a very excellent study. There is one point brought up by Dr. Shaffer that needs emphasis. Fildes, many years ago, pointed out that the mere presence of a positive serologic reaction of the blood of the newborn infant does not of itself warrant a diagnosis of syphilis. In those babies not actually infected, the serologic titer drops from day to day even when high at first and eventually completely fades. In many instances a diagnosis based on the cord blood reaction has resulted in therapy's being given to uninfected children. This Fildes law is not well known to the general practitioner or the obstetrician and should be brought to their attention.

DR. LOREN W. SHAFFER, Detroit: I wish to thank Dr. Wile for his kindness in being so generous to us in his discussion of our paper. He brought out the fact that the drop in the incidence of congenital syphilis that should be expected is seemingly not occurring as far as general nationwide statistics are concerned. I think there are several possible reasons for this: In the first place, it is my impression that the incidence of congenital syphilis as far as new congenital syphilis is concerned must be showing a pronounced reduction. I am sure that is true for the City of Detroit. One of the reasons for the failure to observe such a reduction is that the statistics have not been broken down according to age of the children that are reported as having congenital syphilis. In other words, they are all grouped together whether they have late congenital or infantile congenital syphilis. The other is that the very purpose of prenatal laws requiring blood tests on mothers and stimulating the diagnosis of syphilis in pregnancy and possibly in the children is tending to bring to recognition more cases than formerly were recognized. This is particularly true, as Dr. Chargin brought out, because of the failure of many to recognize that a positive reaction to a test on the blood or on the cord blood of the infant is not necessarily diagnostic, which failure causes more infants to be diagnosed as having congenital syphilis than actually do have it.

In the paper we discuss Rein's conception of serologic interpretation and the difference between the complement fixation and the precipitation tests in the diagnosis of syphilis on the infant. With the complement fixation test, if the mother's blood shows a positive reaction the baby's blood will practically always do so. The precipitation tests will give a positive reaction in the infant in the absence of syphilis in a much smaller percentage of cases, and they are therefore of greater diagnostic significance. This interesting problem in serodiagnosis needs further evaluation.

TREATMENT OF EARLY SYPHILIS WITH PENICILLIN, MAPHARSEN® AND BISMUTH (COMBINED THERAPY)

LOUIS CHARGIN, M.D.
NATHAN SOBEL, M.D.
AND
THEODORE ROSENTHAL, M.D.
NEW YORK

IN THE PRESENT state of our knowledge the treatment of syphilis necessarily resolves itself into the treatment of the disease not as a whole but rather in its various stages. At this time the early and late stages of the disease pose different therapeutic problems. This fact becomes evident when one recalls the disparity in results now obtained by therapy in the different stages of syphilis. The problem of the successful treatment of seronegative primary syphilis can be considered solved, for no matter what schedule of intensive penicillin therapy is instituted, a satisfactory outcome can be expected, with this drug alone, in nearly 100 per cent of the patients treated. Less can be said for the treatment of the disease in the seropositive primary stage. Here the best reported results from penicillin therapy are perhaps no better than success in 92 per cent of the cases. This poorer showing is in part due to the fact that some of the cases regarded as seropositive primary syphilis are already early or even later cases of secondary syphilis. In secondary syphilis the percentage of satisfactory outcome with penicillin is only in the neighborhood of 75 per cent, and with the approach of early latency the proportion of satisfactory results drops even further, to some 66 per cent. It is evident, therefore, that with the increase in duration of the infection the percentage of satisfactory results of therapy shows a progressive decline.

While it is hardly possible to improve on the results now obtained in seronegative primary syphilis, improvement of the effects of treatment in the other stages of the disease is not only desirable but imperative, for unless this is successfully accomplished we will continue to be confronted with the danger of the late manifestations of the disease in the uncured cases.

In considering means of improving the therapeutic results in later syphilis it is of interest to speculate whether fortified therapy, especially that form in which the attack on the disease and/or its organisms is many sided, may not furnish

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From the Bureau of Social Hygiene, Department of Health, City of New York.

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With the technical assistance of Julius H. Pollock, M.D.; Nathan Pensky, M.D.; Moses Silverman, M.D.; Irwin I. Lubowe, M.D.; Jacob Hurowitz, M.D., and Arthur H. Ollswang, M.D.

better results. In experimental syphilis such synergistic treatment has actually accomplished this. Eagle and his co-workers [1] have found that penicillin and oxophenarsine hydrochloride (mapharsen®) are synergistic in the treatment of rabbit syphilis and state that such treatment may be equally synergistic in man. More important is their statement that "the addition of subcurative doses of mapharsen, bismuth, or both, would probably reduce the proportion of treatment failures, and yield therapeutic results well in excess of those possible to achieve with penicillin alone." They furthermore state that "optimum therapy for human syphilis may well consist of penicillin, mapharsen, and bismuth used in combination." Kolmer and Rule,[2] as well as Magnuson and Rosenau,[3] furnish additional evidence of the value of synergistic therapy in animal syphilis.

These experiments indicate that additive treatment does produce better results in animal syphilis, but can we, on that basis alone, unequivocally say the same for human syphilis? Obviously not! It is necessary that actual clinical experience in human syphilis determine this point. Already there have appeared studies dealing with additive treatment in human syphilis.

Eames and Miller [4] gave combined penicillin, neoarsphenamine and bismuth in 1,028 cases of early syphilis, with a total dose of 4,000,000 units of commercial amorphous penicillin plus 6.15 Gm. of neoarsphenamine and 2.2 Gm. of bismuth. In their opinion the results of combined therapy were more satisfactory than those obtained with "commercial penicillin alone."

Pardo-Costello and Pardo [5] administered 10,000,000 units of penicillin in solution plus 10 to 20 bismuth subsalicylate injections to 47 patients and express the opinion that this combined therapy enhanced the value and effectivity of treatment.

Schoch and Alexander [6] gave 1,200,000 units of penicillin in addition to five bismuth subsalicylate injections to patients and are of the opinion that this combination was more effective than penicillin alone, the relapses not only being reduced in number but appearing at a later date.

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1. Eagle, H.; Magnuson, H. T., and Fleischman, R.: The Synergistic Action of Penicillin and Mapharsen (Oxophenarsine Hydrochloride) in the Treatment of Experimental Syphilis, J. Ven. Dis. Inform. **27**:3-9 (Jan.) 1946.

2. Kolmer, J. A.: Penicillin in the Treatment of Experimental Syphilis of Rabbits: II. Synergistic or Additive Activity of Penicillin, Oxophenarsine Hydrochloride and Bismuth Potassium Tartrate, Arch. Dermat. & Syph. **56**:179-186 (Aug.) 1947; IV. The Synergistic or Additive Activity of Penicillin by Oral Administration with Oxophenarsine Hydrochloride ("Mapharsen") by Intravenous and Intramuscular Injection and Bismuth Salicylate by Intramuscular Injection, ibid. **57**:965-974 (June) 1948.

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4. Eames, J. W., and Miller, D. H.: Treatment of Early Syphilis with Penicillin Combined with Neoarsphenamine and Bismuth, Brit. M. J. **2**:672-676 (Sept. 24) 1949.

5. Pardo-Costello, V., and Pardo, O. A.: Treatment of Early Syphilis with Penicillin and Bismuth Subsalicylate: Daily Injection of 500,000 Units of Penicillin G in Sodium Chloride Solution for Twenty Consecutive Days and Ten to Twenty Doses of Bismuth Subsalicylate at the Rate of Two a Week, Arch. Dermat. & Syph. **61**:196-209 (Feb.) 1950.

6. Schoch, A. G., and Alexander, L. J.: Treatment of Early Syphilis with Penicillin, J. A. M. A. **130**:696-698 (March 16) 1946.

McElligott and co-workers [7] treated 275 patients with penicillin, 2,400,000 to 4,000,000 units, neoarsphenamine and bismuth and state their failure rate to have been 4 to 7 per cent.

Rauschkolb and Cole [8] advocate supplemental therapy in order to decrease the relapse rate obtained when penicillin is given alone.

A number of Europeans also advocate combined therapy. In a discussion of recent advances in syphilis therapy, Miescher [9] has expressed the view that arsphenamine-bismuth therapy has not been surpassed by treatment with penicillin and suggests the use of either the former or a combination of the three drugs in the treatment of early syphilis. The French are equally reluctant to dispense with chemotherapy. Merklen and associates [10] state that it is "illogical to use penicillin alone" and recommend combined therapy. They state that in a limited number of cases the early results of combined therapy were entirely satisfactory.

The above-mentioned considerations, experimental as well as clinical, prompted the present study, which had for its object the answer to the question: "Does combined treatment with penicillin, oxophenarsine hydrochloride and bismuth yield better results in early syphilis than that with penicillin alone?"

TABLE 1.—*Distribution of 470 Patients According to Race and Sex*

	Total	White	Nonwhite
Total	470	121	349
Male	259	92	167
Female	211	29	182

PRESENT INVESTIGATION

The study was carried out in the clinics of the Department of Health, City of New York. Of 540 initially admitted unselected patients with early syphilis, 470 completed, or nearly completed, the full course of treatment. These 470 form the basis of this study. The ages varied between 15 and 60 years, and the patients were both males and females. The study covers a period of a little more than two years. Table 1 gives the distribution of the patients by race and sex.

In accordance with the usually accepted classification the cases were divided into (1) seronegative primary, (2) seropositive primary, (3) secondary and (4) early latent syphilis. We are of the opinion that in order for evaluate therapeutic schedules to be evaluated on an equal basis it is essential, at this time, to adhere strictly to this classification. It is also necessary that a uniform serologic "yardstick" for evaluating results be agreed on, one to which all will adhere. Such agreement would lead to more accurate evaluations of results of therapy.

7. McElligott, G. L. M.; Jefferis, F. J. G., and Willcox, R. R.: Treatment of Early Syphilis with Penicillin, Neoarsphenamine and Bismuth, Brit. J. Ven. Dis. **24**:45-49, 1948.

8. Rauschkolb, J. E., and Cole, H. N.: The Treatment of Syphilis with Penicillin in Oil and Wax U. S. P.: Analysis of 153 Cases, Arch. Dermat. & Syph. **60**:676-689 (Nov.) 1949.

9. Miescher, G., in discussion on Treatment of Syphilis with Penicillin, Arch. f. Dermat. u. Syph. **189**:126, 1949.

10. Merklen, F. P., and Vermeil, G.: Traitement antisyphilitique d'attaque de blanchiment rapide pénicilline-arsenical, Paris méd. **37**:54-56 (Feb. 1) 1947. Merklen, F. P., and Nezelof, C.: Essai de traitement accéléré de la syphilis: assaut massif arsenico-bismuthique associé à des doses réduites de pénicilline, Paris méd. **37**:119-120 (March 8) 1947.

Table 2 gives in detail the classification of the 470 cases studied.

The diagnosis was made on positive results of dark field examination of primary or secondary lesions, on secondary lesions and/or serologic reactions and, in the latent cases, on history and serologic reactions.

Treatment consisted in the administration of penicillin G in oil and white wax or of procaine penicillin in aluminum monostearate, given daily for 10 consecutive days (omitting Sundays); the total dose was 6,000,000 units. By far the majority of patients received procaine penicillin. The penicillin therapy was followed by semiweekly intravenous injections of oxophenarsine hydrochloride for 10 successive weeks (dose 0.045 to 0.06 Gm.) and this in turn by 1.5 cc. of a 10 per cent suspension of bismuth in oil for 10 weeks. In some cases the oxophenarsine hydrochloride and bismuth were given concurrently. The entire treatment, therefore, covered a period of from 10 to 16 weeks.

A serologic test for syphilis was performed on all patients at monthly intervals during the first year of observation, and at bimonthly ones thereafter. The serologic test employed in evaluating the success or failure of therapy in this study differed somewhat from that employed by us in two previous studies. While in the previous

TABLE 2.—*Classification of 470 Syphilis Patients According to Diagnosis*

Original Diagnosis	No. of Patients Under Observation	Per Cent
Seronegative primary syphilis	72	15.4+
Seropositive primary syphilis	67	14.1+
Secondary syphilis	170	36.2+
Early latent syphilis	161	34.2+
Total	470	100

series the Mazzini test was employed as the criterion of response to therapy, in this study it served as a screen test and no further testing was required for blood that proved negative by the Mazzini procedure. However, blood found positive to any degree by the Mazzini test was further tested by the Kolmer complement fixation test and by a Venereal Disease Research Laboratory (V D R L) test titered at a level set by Harris. In a recent communication Harris and associates[11] have expressed the view that the V D R L test functions at a satisfactory level of "sensitivity" and "specificity" and, although in a given case the blood with this test may show a negative reaction slightly earlier than it would with the Mazzini technic, the over-all serologic curve of the two tests is about the same. Since the V D R L test is regarded as more specific, it was deemed wise to employ it in evaluating our results.

ANALYSIS OF RESULTS OF TREATMENT

Of the group of 72 persons with primary seronegative syphilis, 70 patients continued to have negative serologic reactions in repeated testing and clinical observation for periods of from eight to 21 months. Table 4 gives the details

11. Harris, A.; Rosenberg, A. A., and Del Vecchio, E. R.: The V. D. R. L. Slide Flocculation Test for Syphilis: II. A Supplementary Report, J. Ven. Dis. Inform. **29**:72-75 (March) 1948.

concerning the observation period. The two remaining persons with seronegative primary syphilis are regarded as showing treatment failures and will be discussed later.

Of the 67 cases of seropositive primary syphilis, 62 (92.5 per cent) became seronegative and 4 (6 per cent) remained seropositive during the period of observation, and in 1 (1.5 per cent) there was either relapse or reinfection.

TABLE 3.—*Analysis of Results of Treatment with 600,000 Units of Penicillin Daily for 10 Days Followed by 10 to 20 Oxophenarsine Hydrochloride and 10 Bismuth Injections*

	No. of Cases	Per Cent of Cases
Seronegative primary syphilis	72	100.0
Remained seronegative	70	97.1
Relapse or reinfection	2	2.9
Seropositive primary syphilis	67	100.0
Became seronegative	62	92.5
Remained seropositive	4	6.0
Relapse or reinfection	1	1.5
Secondary syphilis	170	100.0
Became seronegative	132	77.6
Remained seropositive	37	21.8
Relapse or reinfection	1	0.6
Early latent syphilis	161	100.0
Became seronegative	88	54.6
Remained seropositive	73	45.4
Relapse or reinfection	0	....

TABLE 4.—*Period of Observation of Patients with Primary Seronegative Syphilis*

No. of Patients Observed (Total, 70)	No. of Months of Observation After Treatment
7	8
8	9
7	10
5	11
10	12
8	13
3	14
1	15
7	16
5	17
4	18
2	19
2	20
6	21

In the group of persons with secondary syphilis, totalling 170 patients, 132 (77.6 per cent) became seronegative, 37 (21.8 per cent) remained seropositive during the period of observation and 1 (0.7 per cent) relapsed or became reinfected.

The group with early latent syphilis was comprised of 161 patients. Of these, 88 (54.6 per cent) became seronegative and 73 (45.4 per cent) remained seropositive.

Examining the figures as a whole, one notes the progressive decline in satisfactory outcome with the increase in the duration of the infection—97.1 per cent, 92.5 per

cent, 77.6 per cent and 54.6 per cent in the various classifications, respectively. This is a characteristic observed in previous studies, and combined treatment as herein discussed has provided no exception to the rule.

In a previous study,[12] of treatment of syphilis patients for 16 days with penicillin, it was demonstrated that the earlier in the disease that patients were placed under appropriate treatment, the faster the serologic reversal. Thus the seropositive primary cases took four months to become seronegative as contrasted with the secondary and latent forms of the disease, which required 10 months for seronegativity. A similar evaluation in our present study shows identical results; the very early syphilis cases become seronegative much sooner than the secondary and latent ones. One must conclude, therefore, that combined therapy shows no advantage in this respect over penicillin given alone.

REACTION

During the first few months of our study penicillin injection in oil and wax of the fluid variety was employed in treatment, and during this period approximately 10 per cent of the patients showed reactions. Later, with a change to procaine penicillin there was a remarkable drop in reaction to about 1 per cent. The types of penicillin reactions observed were chiefly urticarial, immediate or delayed, contact type dermatitis and activation of fungus sites. For none was it found necessary, except for a short period, to interrupt treatment.

The arsenical toxicodermas were relatively few, although some were severe. There were no fatalities.

SPINAL FLUID EXAMINATION

Up to the time of the preparation of this report 267 patients were subjected to lumbar puncture a year or longer after penicillin therapy. None was found to show abnormalities.

RELAPSE OR REINFECTION

Only four relapses or reinfections were observed, and, since they were so few, a short account will be given of each. Two occurred in cases of seronegative primary syphilis and one each in cases of seropositive primary and secondary syphilis.

Case 1.—C. J., a Negro, was admitted with a primary lesion on the frenum, positive on dark field examination. The reaction of the blood was negative. The patient received 6,000,000 units of penicillin in oil and wax plus 15 oxophenarsine hydrochloride injections. Treatment was completed in two months. The patient lapsed from observation for four months, and when he returned the serologic reaction was 4 +, with a VDRL titer of 1:40. He also presented a generalized eruption. Repeated sexual exposure during the lapsed period was admitted. The case was regarded as showing a treatment failure rather than reinfection.

Case 2.—H. H., a male Negro aged 22, was diagnosed as having seronegative primary syphilis. Lesions were positive on dark field examination. The man received 6,000,000 units of penicillin and 11 oxophenarsine hydrochloride injections. The serologic reaction remained negative for four months after penicillin therapy, and the patient lapsed from observation. Ten months later the Kolmer reaction was anticomplementary with a VDRL titer of 1:40. Exposure was admitted. The development was regarded as a serorelapse in seronegative primary syphilis.

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12. Chargin, L.; Sobel, N.; Rein, C., and Rosenthal, T.: Treatment of Early Syphilis with Penicillin Injection in Oil and Wax U. S. P.: Report of 153 Cases, Arch. Dermat. & Syph. **59**:595-605 (June) 1949.

CASE 3.—A. S., a male Negro aged 30, was admitted with a diagnosis of secondary syphilis. He was treated with 6,000,000 units of penicillin and 20 oxophenarsine hydrochloride and 10 bismuth injections. The original serologic reaction was 4+, and the VDRL titer, 1:10. The reaction became negative in seven months. Five months later it was still negative. Seven months thereafter the Kolmer reaction was 4+, and the VDRL titer, 1:10. No clinical signs were present. The case was regarded as showing serorelapse.

CASE 4.—D. M., a white man aged 41, had seropositive primary syphilis with lesions positive on dark field examination. He was treated with 6,000,000 units of penicillin and 20 oxophenarsine hydrochloride and three bismuth injections in a period of three months. He lapsed from observation for 17 months and on return presented a primary lesion on the corona at a site different from that of the first lesion. The lesion was positive on dark field examination; the Kahn reaction was 4+, and the VDRL titer was 1:2, which rose to 1:10 in two weeks. This case very likely showed reinfection.

As is well known, it is frequently impossible to decide the question of whether relapse or reinfection is present in a given case, but on the basis of the usual criteria of reinfection, case 4 and perhaps case 2 may be classified as showing it. We nevertheless regard all four cases as showing treatment failure, and our failure rate is accordingly 0.85 per cent.

SEROLOGIC TITER

The behavior of the serologic titer in the cases that remain seropositive shows little difference in this series from that observed with the 16 day penicillin schedule.

There were four cases of seropositive primary syphilis in which there was still a positive reaction eight months after therapy. However, all four showed a satisfactory trend. The titer dropped from 1:40 to 1:2 in one, from 1:20 to 1:2 in another and from 1:10 to 1:2 in the remaining two cases. Complete serologic reversal will probably occur in all in a relatively short time.

The figures for those with secondary syphilis show that there were 37 cases, of a total of 170, in which seronegativity was not attained. The serologic titer in 31, or 83.8 per cent, of these showed a satisfactory trend, while in 6, or 16.2 per cent, it did not. The original titer in most was relatively high—1:20 to 1:320—and its drop in some was striking—from 1:320 to 1:1, and from 1:80 to 1:20. With time, no doubt many of these persons will also become seronegative.

In 56, or 76.7 per cent, of the cases of latent syphilis there was a satisfactory trend while in 17, or 23.3 per cent, there was not. Again, the initial titer in most was relatively high but no higher than in the secondary group. No doubt a percentage will become negative in time, as with similar cases reported by Kaplan and Brightman [13] and by Moore.[14]

COMPARISON OF RESULTS

The 16 day schedule of treatment of early syphilis with penicillin, as reported by our group,[12] gives therapeutic results which are on a par with the best schedules reported. It is, therefore, being used for comparison with the present com-

13. Kaplan, B. I., and Brightman, I. J.: Studies on Therapeutic Procedures in Latent and Late Syphilis: Quantitative Serologic Titers Following Intensive Mapharsen Drip Therapy in Latent Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **28**:192-199 (March) 1944.

14. Moore, J. E.; Kemp, J. E., and others: The Modern Treatment of Syphilis, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1941, p. 263.

bined schedule. Table 5 gives a summary and comparison of the two. It will be noted that in seronegative primary syphilis the advantage is in favor of the 16 day schedule, with a 100 per cent satisfactory outcome as compared with 97.1 per cent for combined therapy. This advantage is only apparent, since the results in the 16 day schedule are based on only 13 cases as compared with 72 cases in the present study. It is very likely that the observations here reported, based as they are on a larger series, give a truer picture of results. In the group with seropositive primary syphilis and in that with secondary syphilis the satisfactory results are almost identical. Data on patients who remained seropositive in both classifications likewise do not show material differences. It is in the relapse and reinfection group that the difference is so striking—a relapse rate of 3.9 per cent with the 16 day

TABLE 5.—*Summary and Comparison of Results of Therapy with Penicillin Alone and with Penicillin Plus Arsenic and Bismuth Preparations*

	300,000 Units of Penicillin Daily for 16 Days (Total Dosage, 4,800,000 Units)		600,000 Units of Penicillin Daily for 10 Days Followed by 10 to 20 Oxophenarsine Hydrochloride and 10 Bismuth Injections	
	No. of Cases	Per Cent of Cases	No. of Cases	Per Cent of Cases
Seronegative primary syphilis	13	100.0	72	100.0
Remained seronegative	13	100.0	70	97.1
Relapse or reinfection	0	0.0	2	2.9
Seropositive primary syphilis	51	100.0	67	100.0
Became seronegative	47	92.2	62	92.5
Remained seropositive	2	4.0	4	6.0
Relapse or reinfection	2	4.0	1	1.5
Secondary syphilis	83	100.0	170	100.0
Became seronegative	62	74.7	132	77.6
Remained seropositive	17	20.5	37	21.8
Relapse or reinfection	4	4.8	1	0.6
Early latent syphilis	6	100.0	161	100.0
Became seronegative	4	66.7	88	54.6
Remained seropositive	2	33.3	73	45.4
Relapse or reinfection	0	....	0	....

schedule against one of 0.85 per cent with combined therapy. This observation is perhaps the most significant one in the study.

SUMMARY

The a priori expectation of a higher "cure" rate with combined therapy has not been realized, since the satisfactory outcomes in the four classifications in this study and in previous ones with penicillin alone are about the same. The same statement holds true for the cases which remained seropositive—the results were no better, and no worse.

The remarkable difference is noted in the relapse and reinfection rate, which with the 16 day schedule is 3.9 per cent as compared with 0.85 per cent with combined therapy. If this lower rate with combined therapy is confirmed by further study it will weigh strongly in favor of the effectiveness of combined therapy, at least from the standpoint of relapses.

So far as the effect on the clinical manifestations is concerned, both schedules, of course, furnish highly satisfactory results. With respect to long term results,

i. e., the prevention of central nervous system and cardiovascular syphilis, we already know that chemotherapy does prevent these. We are less certain respecting this point in the case of patients who receive penicillin alone. Nevertheless there is reason to believe even at this time that those persons with syphilis who show a satisfactory response to penicillin alone are likely, in nearly all instances, to escape the late manifestations.[15] Definite information will have to await further observation.

If we are to judge by the experience gained in this study, in seronegative primary syphilis combined treatment of the type discussed is not necessary; in later early syphilis it appears to be of doubtful value.

Whether synergistic treatment with the newer antibiotics will yield better results than are now obtained in later early syphilis is a matter for future determination.

At this time it is still necessary to discover cases of syphilis in the seronegative primary stage in order to obtain optimum results from therapy.

CONCLUSIONS

Treatment schedule consisting in the administration of 6,000,000 units of penicillin, 10 to 20 injections of oxophenarsine hydrochloride and 10 injections of bismuth subsalicylate (combined schedule) was employed in 470 cases of early syphilis.

Comparison of the results obtained with the combined schedule of therapy with those secured with the 16 day schedule in which penicillin alone is employed reveals that the satisfactory outcome in the two is about the same. This statement also holds true with respect to the cases that remained seropositive in the two schedules.

The outstanding difference was the low relapse rate with the combined schedule —0.85 per cent, as compared with 3.9 per cent with the 16 day plan. If further study confirms this observation it should weigh heavily in favor of combined therapy in early syphilis as herein discussed.

1 West Eighty-Fifth Street (Dr. Chargin).

124 East Fortieth Street (Dr. Sobel).

1 West Ninety-First Street (Dr. Rosenthal).

ABSTRACT OF DISCUSSION

Dr. Norman N. Epstein, San Francisco: Dr. Chargin and his associates have made an important contribution to the subject of the treatment of early syphilis. They have found no advantage in combining 10 weeks of treatment with arsenic and bismuth preparation with penicillin therapy over using penicillin alone. This work definitely settles the point and should cause the elimination of arsenic and bismuth preparations from initial treatment schedules for untreated acute syphilis and early latent syphilis. The removal of arsenicals from the treatment of early syphilis is particularly acceptable because of the increased hazards of arsenical therapy.

Their observations, however, bring up some interesting points for discussion. They noticed that the clinical relapse rate in this group of patients treated with arsenic and bismuth preparations and penicillin was significantly lower than that in a previous series of patients treated with penicillin alone, that is, 0.85 per cent and 3.9 per cent, respectively. The authors consider this point an important one and are inclined to attribute the difference to the superior therapeutic value of the combined treatment. This explanation may or may not be true. The lower incidence of reinfection was probably due to the fact that the post penicillin

15. Mahoney, J. F.: Quarterly Bulletin, New York City, Department of Health, (Spring) 1950, page 1, vol. 18.

therapy was continued for 10 weeks. The patients, therefore, were protected against contact infection by the spirocheticidal effects of the arsenic and bismuth preparations during the entire period of treatment. The cycle of "ping-pong" syphilis may have been broken by the time element alone. These patients may have lost contact with their originally infected partners or with those whom they themselves had infected. Furthermore, these individuals may have been brought under treatment during that period. The decreasing incidence of early infectious syphilis may also be a factor in the low clinical relapse rate reported here.

The authors point out that the curative effects of penicillin in the treatment of early syphilis are not as impressive as is generally thought. They report from the literature that cure rates decrease as the duration of the disease increases. In seronegative primary syphilis the cure rate is approximately 100 per cent; in seropositive primary syphilis, 92 per cent; in secondary syphilis, 75 per cent, and in early latent syphilis, 66 per cent. Cure rates in their own series were 97.1 per cent, 92.5 per cent, 77.6 per cent, and 54.6 per cent, respectively. These observations indicate that early syphilis behaves with penicillin as it did with chemotherapy: the longer the disease has been established, the less effective is therapy. This point suggests that we may be disappointed in the ultimate outcome in cases of late latent and late syphilis treated with a single course of penicillin.

One may disagree with the authors with regard to the cure rates which they report because they do not include in these figures those patients in whom the serologic titers were decreasing satisfactorily. They admit that they expect many of these persons to become seronegative eventually. Therefore, their cure rates will very likely have to be adjusted upward.

Another important observation in the paper was the fact that of 267 patients who had had a spinal fluid examination one or more years after their treatment none showed abnormalities. This proves again that penicillin is very effective in preventing and eradicating neurosyphilis in patients with early syphilis.

At the San Francisco City Clinic since 1945 all patients with early syphilis have been treated with 10 injections of 300,000 units each of calcium penicillin in peanut oil containing 4.8 per cent white wax, for a total of 3,000,000 units. Of 481 patients so treated, 58 had no follow-up and 280 have been followed for from nine to 54 months. The failure rate for this group was 18.2 per cent; 62 persons required re-treatment. This work has been done under the direction of Dr. Richard Koch, and an account of it will be published in detail.

The suggestion of the authors that penicillin given in combination with other antibiotics such as aureomycin and chloramphenicol (chloromycetin®) may give superior therapeutic effects appears to be an excellent one.

DR. CHARLES C. DENNIE, Kansas City, Mo.: It seems that in the treatment of early syphilis with penicillin the therapeutists toyed with the so-called ping-pong infections, or, as they call them, reinfections. I believe there is one phase of this subject that has never been investigated. I wish that someone would take the group of patients who have been rendered seronegative and see how many reinfections there are in that group. If the rule holds true that presence of infection noted again means reinfection because the syphilis has been eradicated by the penicillin, there ought to be as many reinfections in these persons after their syphilis has been cured as there were infections before any treatment was instituted at all.

Now, my impression from looking over these patients is that the rate of reinfection of patients who have been cured of their syphilis is practically nil.

DR. STEPHEN ROTHMAN, Chicago: I have always wondered whether it makes much difference whether a course of penicillin is given alone or in combination with a few arsenical and bismuth injections. I am afraid that neither method is satisfactory.

At the April meeting on "Latest Advances in the Study of Venereal Diseases," held under the auspices of the United States Public Health Service in Washington D. C., once again the results of treatment of early syphilis with a single course of penicillin injections (2,500,000 to 6,000,000 units) were praised with great optimism although by now the number of cases requiring re-treatment is around 30 per cent. The statisticians have resigned themselves to the fact that they are unable to differentiate relapses and reinfections, and, therefore, with scientific rigorousness, they count them all as relapses. However, if you call their attention to the fact that a relapse rate of 30 per cent is frighteningly high and that the old long term treatment schedule gave much better results, they reassure you that these 30 per cent are

overwhelmingly reinfection anyhow. The percentage of relapses is growing as time passes by. It has been claimed that if a patient with early syphilis remains free from relapses clinically and serologically for two years he can be regarded as cured. I am still looking for evidence which would support this view. Nobody can be sure how many of these patients will have late manifestations in the coming years. Therefore, in my clinic we follow up the initial penicillin course with arsenic and bismuth therapy and treat every patient according to the classic schedule for two years, except in cases of seronegative primary syphilis. I was happy to hear Dr. Dennie's similar conservative view in his presidential address. With regard to the superior qualities of penicillin in antisyphilitic treatment, it is regrettable that nobody has tried to work out schedules for a chronic-intermittent treatment with penicillin. Without convincing reasons it has been taken for granted that early syphilis can be aborted by one course of penicillin injections.

Dr. O'Leary has stated that it is problematic whether or not the present decrease in incidence has anything to do with modern treatment methods. The tremendous increase of new infections in Germany after the first world war was followed in the middle twenties by a considerable fall. Everybody attributed this drop to the effectiveness of the so-called maximal therapy with its large doses of arsenicals and heavy metals, a daring innovation at that time. However, as soon as social, political and economic conditions became more uncertain in the late twenties the incidence rose steeply once more although the type of treatment did not change.

Dr. Louis Chargin, New York: I am grateful to the discussants for their remarks. As time progresses some of our cases now still seropositive will likely fade out; on the other hand, some now seronegative may become seropositive. These results will in the end probably balance each other, and the satisfactory outcome as presented is not likely to be materially changed.

The 18 per cent relapse rate mentioned by Dr. Epstein seems rather high and perhaps can be attributed to inadequate dosage.

While it is proper to experiment with low dose therapy, at this time it is our duty to insist that the general practitioner employ large doses in treating his cases, at least 300,000 units of penicillin daily for a 16 day period. Thus relapses will largely be avoided. I should like to reiterate my opinion, based on our experience, that additive chemotherapy does not show a higher rate of "cure" than does penicillin given alone. Combined treatment with penicillin and arsenic and bismuth preparations does show a lower relapse rate. The meaning of this observation is not yet clear; time will tell. If the relapse rate remains low with additive treatment, this method should become standard therapy.

Dr Rothman fears that the long term results with penicillin alone will not be as satisfactory as those shown by chemotherapy. I can state from extensive observation that the behavior pattern of syphilis treated with penicillin alone exactly duplicates that seen with the best methods of chemotherapy. Furthermore, I should like to venture the opinion that the long term results that are obtained from chemotherapy will be paralleled by penicillin treatment if that drug is given in adequate dosage.

PARAAMINOBENZOIC ACID IN DERMATITIS HERPETIFORMIS

CHRIS J. D. ZARAFONETIS, M.D.
PHILADELPHIA
EDGAR B. JOHNWICK, M.D.
LEWIS W. KIRKMAN, M.D.
AND
ARTHUR C. CURTIS, M.D.
ANN ARBOR, MICH.

THE ADMINISTRATION of large doses of paraaminobenzoic acid (PABA) has been shown to benefit a variety of clinical disorders. These include the rickettsioses,[1] lymphoblastoma cutis,[2] lupus erythematosus,[3] dermatomyositis [4] and scleroderma.[4] The purpose of this report is to describe the results of paraaminobenzoic acid treatment in still another condition, namely, dermatitis herpetiformis. The reason for undertaking a trial of paraaminobenzoic acid therapy in dermatitis herpetiformis had its origin in the study of the effect of paraaminobenzoic acid in lupus erythematosus.[3b,c] It will be recalled that lupus erythematosus is often associated with hypersensitivity to sunlight. Similarly, patients receiving sulfonamide drugs not infrequently manifest sunlight sensitivity. Since paraaminobenzoic acid and sulfonamides are metabolite antagonists, it was reasoned that paraaminobenzoic acid might have an opposite and beneficial effect in lupus erythematosus. This hypothesis was tested clinically, and, in view of the results observed in certain patients with this disorder, it was decided to try paraaminobenzoic acid in other conditions in which light hypersensitivity might be a factor. This thought was in mind when a patient with extensive dermatitis herpetiformis remarked to one of us (E. B. J.) that exposure to sunlight increased the activity and discomfort of her lesions. Since she no longer responded to the usual forms of therapy, it was decided

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From the Department of Internal Medicine and Dermatology and Syphilology, University of Michigan Medical School.

1. Snyder, J. C.: Treatment of the Rickettsial Diseases of Man, in Rickettsial Diseases of Man, a Symposium, Washington (1946), American Association for Advancement of Science, 1948.

2. (*a*) Zarafonetis, C. J. D.: Therapeutic Possibilities of Para-Aminobenzoic Acid, Ann. Int. Med. **30**:1188-1211, 1949. (*b*) Zarafonetis, C. J. D.; Curtis, A. C., and Kirkman, L. W.: Para-Aminobenzoic Acid in Lymphoblastoma Cutis and Mycosis Fungoides, to be published.

3. (*a*) Zarafonetis.[2a] (*b*) Zarafonetis, C. J. D.; Curtis, A. C., and Grekin, R. H.: The Effects of Para-Aminobenzoic Acid in Lupus Erythematosus: Preliminary Report, Univ. Hosp. Bull., Ann Arbor **13**:122-125, 1947. (*c*) Zarafonetis, C. J. D.; Grekin, R. H., and Curtis, A. C.: Further Studies on the Treatment of Lupus Erythematosus with Sodium Para-Aminobenzoate, J. Invest. Dermat. **11**:359-379, 1948.

4. Zarafonetis.[2a] Zarafonetis, C. J. D.; Curtis, A. C., and Gulick, A. E.: Use of Paraaminobenzoic Acid in Dermatomyositis and Scleroderma, Arch. Int. Med. **85**:27-43 (Jan.) 1950.

to administer a trial course of paraaminobenzoic acid. The gratifying response observed in this case led to the treatment of additional patients with dermatitis herpetiformis. Below are given case reports on 16 patients who have received paraaminobenzoic acid [5] therapy for this condition.

REPORT OF CASES

CASE 1.—O. B., a white housewife aged 58, entered the University Hospital for the first time on June 4, 1947. Five weeks previously a patch of clear, tense, pruritic and burning vesicles had suddenly appeared on the anterior aspect of the thorax, and within four days the condition became rather generalized except for the face and mucous membranes. Some of the vesicles enlarged to form bullae; some of the bullae coalesced to produce palm-sized patches; others ruptured, leaving smooth, weeping, erythematous bases or crusted surfaces. New lesions appeared in crops, involving new skin or the margins of intact or ruptured bullae. Constitutional symptoms were minimal aside from the intense burning and pruritus, which was especially pronounced at night. Diagnoses prior to admission were varicella, originally, and then pemphigus vulgaris. Treatment had consisted in the administration of an antihistamine drug by mouth, along with local application of wet dressings, lotions and ointments.

Physical examination revealed a fairly well developed and nourished middle-aged white female who was obviously uncomfortable but neither acutely nor chronically ill. Except for the skin, no abnormality was found. There was a symmetrical patchy, bullous and vesicular eruption, with grouping of lesions, involving the neck, trunk, axillas, inguinal folds, external genitalia, extremities and, sparingly, the scalp. Various stages of involution and evolution were present. All new lesions were tense, clear vesicles, some arising from apparently normal skin and others having erythematous bases or being surrounded by bright red halos. Some bullae were tense and contained clear fluid; others were flaccid sacs with milky, serosanguineous or hemorrhagic contents. There were recently ruptured lesions with smooth, exuding surfaces or crusted tops. Discrete vesicles, pustules and erosions were found on the scalp. Residual circinate, configurate, confluent and iris-like patches of erythema or hyperpigmentation were present on the feet, legs, thighs and trunk. There were no lesions on the face, and the mucous membranes of the eyes, mouth, nose, anus and vagina were normal. Nikolsky's sign was not elicited. There was only minimal lymphadenopathy of the inguinal, axillary and neck glands.

Chest roentgenograms, the Kahn test and repeated urinalyses revealed no abnormality. Blood examinations showed normal hemoglobin and erythrocyte levels. Leukocyte counts varied from 17,000 to 26,000 with 22 to 36 per cent eosinophils. Fluid from clear bullae showed numerous eosinophils and polymorphonuclear cells. Total serum proteins and the albumin-globulin ratio were normal. Biopsy showed an acute inflammatory process of the corium, with numerous eosinophils in the infiltrate and vesicle formation lifting off the entire epidermis.

A diagnosis of dermatitis herpetiformis bullosa was made, and treatment was started with colloidal baths twice daily, continuous wet dressings to all moist areas between baths, a high protein diet, infusions of plasma daily (500 cc.) and 1 Gm. each of sulfapyridine and sodium bicarbonate every four hours, six times daily. Improvement was immediate. Within three days the pruritus had subsided and there were very few new lesions developing. Five days later the patient became quite cyanotic, complained of intense nausea and commenced vomiting. Sulfadiazine was substituted for the sulfapyridine, and within 24 hours there was recurrence of the pruritus, followed by crops of new vesicles. Sulfapyridine and sodium bicarbonate, 4 Gm. daily of each along with 50 mg. of tripelennamine (pyribenzamine®) hydrochloride, were given in place of the sulfadiazine, and regression of lesions and pruritus occurred promptly. The patient was discharged from the hospital in good condition, with all lesions healed or healing. She was advised to continue the same therapeutic program at home, along with baths and local applications of an antipruritic lotion.

5. Paraaminobenzoic acid was administered to these patients as potassium paraaminobenzoate (KPAB) and sodium paraaminobenzoate (NaPAB). Generous quantities of these compounds were contributed for use in this study by B. L. Lemke & Company, Lodi, N. J.; Merck & Company, Inc., Rahway, N. J., and Wyeth, Inc., Philadelphia.

She was next seen and readmitted on July 1, 1947. After discharge she had done well for only three days and then had acquired successive crops of vesicles and bullae in the same general regions previously involved. On her second admission she was not apparently ill. The skin showed residual patches of hyperpigmentation, erythema, pustules, bullae, ruptured bullae and new grouped, tense vesicles. The axillas and inguinal and vulvar regions were severely involved, and there was secondary pyogenic infection with vegetations and elevated erythematous plaques resembling condylomata lata. New vesicles again were present in older lesions, but no mucous membranes were involved. There was only minimal lymphadenopathy. Results of urinalyses, hemoglobin estimations and erythrocyte counts were normal. Leukocyte counts ranged from 17,000 to 24,000 with 48 to 52 per cent polymorphonuclear neutrophils, 26 to 30 per cent eosinophils, 12 to 16 per cent lymphocytes and 6 to 10 per cent monocytes. Total serum proteins were 5.2 Gm. per 100 cc. with an albumin-globulin ratio of 2.0.

Treatment was again initiated with 1 Gm. each of sulfapyridine and sodium bicarbonate, six times daily, every four hours; 100 mg. of tripelennamine hydrochloride, four times daily; colloidal baths; wet dressings, and a high protein diet. After five days the patient showed little change and was unable to retain fluids or food because of intense nausea. The amount of sulfapyridine given was reduced to 4 Gm. daily, and after three days use of the drug had to be discontinued entirely. Intravenously administered fluids, infusions of plasma and a whole blood transfusion were given, and in three days the patient was able to retain food and fluids by mouth. The administration of asiatic pills (arsenic trioxide, 0.007 Gm.) three times daily, along with tripelennamine, 100 mg. four times daily, resulted in subsidence of pruritus, and the eruption again cleared. The patient was then given two exposures of superficial roentgen irradiation to the axillas, vulva, neck, thighs and legs. On July 23, 1947, she was discharged in good condition with only residual hyperpigmentation remaining at the formerly involved areas and was advised to continue taking asiatic pills and tripelennamine hydrochloride, as prescribed, for one month.

She remained comparatively well for approximately two months, with only an occasional new vesicle appearing, and then suddenly acquired an acute vesicular and bullous outbreak involving the feet, neck, axillas and thighs, associated with chills, fever and general malaise. Pruritus and burning of the lesions were severe. Physical examination revealed nothing of consequence except the cutaneous eruption and gingivitis and periodontoclasia involving one tooth. She was advised to have a thorough dental examination and treatment of the tooth and gums. She was again given sulfadiazine, 4 Gm. daily, and advised to resume the colloidal baths and wet dressings to all moist areas. One week later she had a generalized bullous eruption involving all sites previously affected. The use of tripelennamine hydrochloride, 50 mg. every three hours, and an antipruritic lotion, in addition to the sulfadiazine and baths, was advised, but little improvement was noted after one week.

On Oct. 27, 1947, all other medications were discontinued and a trial of paraaminobenzoic acid therapy begun for reasons previously discussed. The patient received 2 Gm. of sodium paraaminobenzoate every two hours during the day for eight doses and 4 Gm. at midnight. She was advised that the lesions might flare up initially, as they did, shortly after the administration of sodium paraaminobenzoate was begun. Treatment was continued, however, and within three weeks the lesions had largely cleared. The dosage was changed to six doses of 3 Gm. each during the day. Pruritus subsided, and the cutaneous lesions were completely suppressed. After the skin had remained clear for several weeks, the patient discontinued the medication. Within two weeks a vesicular eruption developed on the forearms, arms, shoulders, axillas, trunk, thighs, legs and ankles. It was similar to that seen originally. There were no constitutional symptoms, but local pruritus and burning were intense. The appearance of the lesions on the thighs on Feb. 3, 1948, is shown in figure 1 *A*. Treatment with sodium paraaminobenzoate was reinstituted; within one week the pruritus had subsided, and the lesions cleared after the third week. There was some residual hyperpigmentation, however, even two months later, as can be seen in figure 1 *B*.

The patient continued to take sodium paraaminobenzoate until she had an upper respiratory tract infection followed by a severe gastrointestinal upset. Treatment was stopped, and within three weeks an extensive characteristic relapse followed. The patient then resumed paraaminobenzoic acid therapy on May 26, 1948. It was found that she could tolerate a half and half mixture of potassium and sodium paraaminobenzoate better than sodium salt alone.

During the next seven months, the patient continued on treatment with 15 to 18 Gm. daily and the condition remained in clinical remission. She began reducing the amount further in January 1949, first to 12 Gm. daily and then to 9 Gm. On treatment with the lower dose she had occasional isolated vesicles which were transitory. She preferred this relatively minimal discomfort to taking larger amounts of paraaminobenzoic acid. By June 30, 1949, her skin was practically normal in appearance; even the areas of hyperpigmentation had faded. Treatment was deliberately discontinued to see whether relapse would follow. Within two weeks isolated lesions began to appear, and by July 29 the recurrence was quite extensive. The involvement

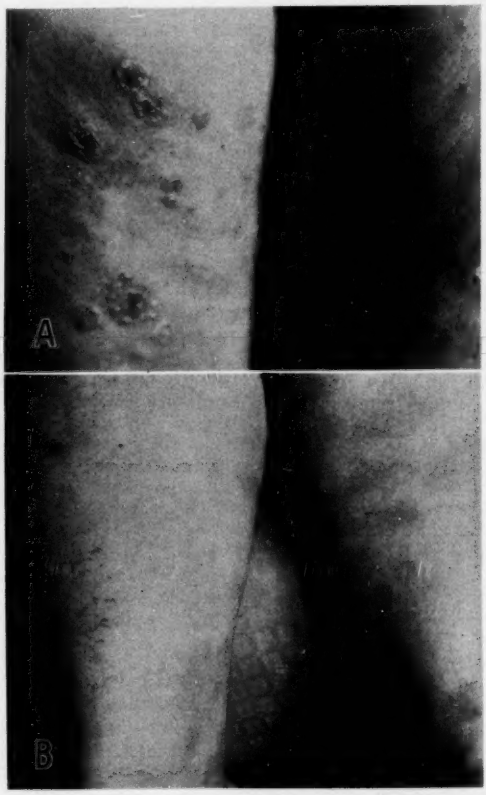

Fig. 1.—*A*, lesions on thighs in case 1 on Feb. 3, 1948. They were part of the relapse observed after the patient stopped the first course of paraaminobenzoic acid therapy. *B*, the same region photographed April 2, 1948, two months after resumption of paraaminobenzoic acid therapy.

of the popliteal spaces is seen in figure 2 *A*. An experimental trial of chloramphenicol (chloromycetin®) therapy was begun, 4 Gm. daily being administered. After a total of 19 Gm. of chloramphenicol had been taken the patient had to stop its use because of severe diarrhea, soreness of the mouth and lips and burning sensation of the stomach and rectum. Within a few days the reaction had subsided and chloramphenicol was tried again in much reduced amounts. This dosage was followed by a similar reaction, and the use of the drug was therefore discontinued again.

On August 8 potassium and sodium paraaminobenzoate therapy was reinstituted. The activity of the dermatitis herpetiformis was about the same as at the beginning of the trial of chloramphenicol. There was a mild exacerbation of lesions for about one week, and then improvement followed. By August 30 only the erythematous bases of former lesions remained. Control was maintained by 12 Gm. daily of the compound. Photographs were taken on Nov. 29, 1949, and revealed only residual hyperpigmentation (fig. 2 *B*). Since that time until the most recent visit, on May 25, 1950, the patient continued to take 9 to 12 Gm. a day of the paraaminobenzoic acid salts. Satisfactory suppression of the process was maintained throughout that time.

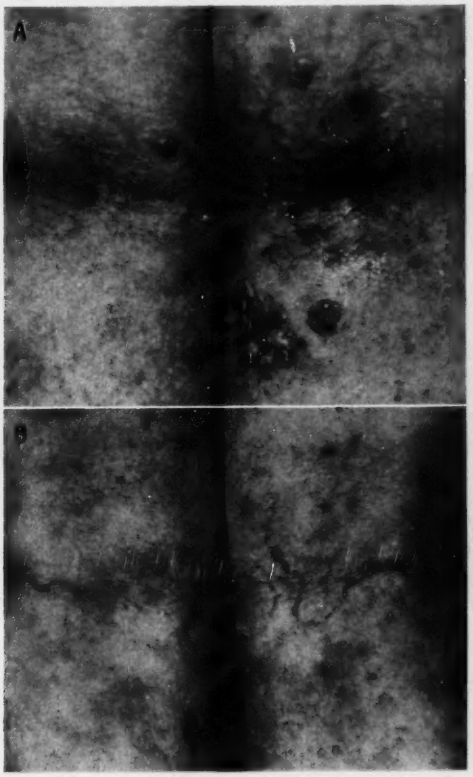

Fig. 2.—*A*, popliteal involvement in case 1 on July 29, 1949, part of the relapse observed after cessation of paraaminobenzoic acid treatment on June 30. *B*, same region on Nov. 29, 1949. Administration of paraaminobenzoic acid had been resumed on August 8.

Case 2.—P. J. M., a white, married 30 year old machinist, acquired a pruritic papulovesicular eruption on the trunk, buttocks, arms, axillas, thighs and legs in January 1947. Treatment with sulfadiazine by mouth for one month and intravenous injections of an arsenical preparation at weekly intervals for another month had produced no relief. The patient was first seen in the Department of Dermatology on July 7, 1947.

Physical examination revealed no abnormality except for the skin, and the patient did not appear to be either acutely or chronically ill. There was a widespread papulovesicular eruption arranged in groups and symmetrically disposed, involving the arms, shoulders, axillas, trunk,

buttocks, thighs and legs. Excoriations were numerous and confirmed the pruritic nature of the eruption. Patches of hyperpigmentation, in which healed lesions and scarring appeared, were present adjacent to and between active patches. There were no mucosal lesions, and the scalp was clear.

The reaction to the Kahn test on the blood serum and the chest roentgenogram were negative. Results of blood studies and urinalyses were within normal limits.

A diagnosis of dermatitis herpetiformis was made, and treatment was started with asiatic pills (arsenic trioxide, 0.007 Gm.) three times daily, superficial unfiltered roentgen radiation to the affected areas and an antipruritic lotion. There was only minimal improvement noted in six weeks. Tripelennamine hydrochloride, 50 mg. four times daily, was then prescribed, in addition to the asiatic pills, and two weeks later, because there had been no noticeable improvement, diphenhydramine (benadryl®) hydrochloride was substituted for the tripelennamine hydrochloride. The patient received two additional exposures to roentgen radiation at two week intervals, and on Oct. 2, 1947, was much improved, having less pruritus and few new lesions. Two weeks later the skin eruption had almost entirely cleared. On Nov. 6, 1947, the

Fig. 3.—*A*, left axillary involvement in case 2, Dec. 3, 1947, prior to institution of paraaminobenzoic acid therapy. *B*, the same area on Feb. 2, 1948.

patient was seen with a recurrence of the vesicular eruption and complained of intense pruritus, especially at night. Treatment with 1 Gm. of sulfathiazole given four times daily, baths and local applications of an antipruritic lotion produced no improvement in three weeks.

On Dec. 3, 1947, pretreatment photographs (fig. 3*A*) and a biopsy of a typical papulovesicular lesion were taken. The biopsy was histologically compatible with dermatitis herpetiformis. The patient was then started on treatment with sodium paraaminobenzoate, 20 cc. of a 10 per cent solution given every two hours during the day and 40 cc. at 12 p. m. and 4 a. m. Two weeks later he had a number of new lesions but the pruritus had subsided considerably. There was, in addition to the papulovesicular eruption on the trunk and extremities, a moderately severe seborrheic dermatitis involving the scalp and face. Local treatment with shampoos and with sulfur and salicylic acid ointment was advised. On Jan. 5, 1948, the seborrheic dermatitis had almost entirely cleared and the patient reported that only a few new lesions had developed. The pruritus was minimal. By January 19 the eruption had cleared except for hyperpigmentation of the previously involved areas. The patient stated that he felt fine and had gained weight. He was advised to continue with his medication for two weeks and then stop treatment. He was next seen on Feb. 2, 1948. He had no new lesions

(fig. 3*B*), was completely free of pruritus and had gained 6 pounds (3 Kg.) in the past month. A biopsy taken from a site adjacent to the first one was reported as showing normal characteristics.

The sodium paraaminobenzoate therapy was discontinued on Feb. 2, 1948, and the patient was advised to return in the event of relapse. By February 16 there was a recrudescence of lesions accompanied with pronounced pruritus. Treatment with sodium paraaminobenzoate was resumed, and suppression of the process was again achieved in about three weeks' time. Treatment was maintained at 24 Gm. daily until June 9, 1948, with adequate control of the dermatitis herpetiformis. It was then decided to attempt intermittent therapy, and the sodium paraaminobenzoate was omitted for five days. Although the skin was still clear when use of the drug was resumed, pruritus and scattered lesions occurred a few days later. These gradually subsided, and the patient subsequently remained on treatment with 20 to 24 Gm. daily of sodium paraaminobenzoate during the next 17 months. He failed to return on schedule for a supply of medication in November 1949 and had a moderate relapse by December 16. Resumption of therapy was again followed by subsidence of the process. The patient remained clear of lesions until March 16, 1950, at which time he was starting to have a relapse because his supply of sodium paraaminobenzoate had been exhausted 10 days before. Treatment was withheld for an additional 10 days, and lesions and pruritus progressively increased during that period. Therapy was resumed on March 27, and control of the disorder was reestablished in about two weeks. The patient continued on treatment with 18 to 24 Gm. per day of sodium paraaminobenzoate through May 19, 1950, the date of his most recent clinic visit.

CASE 3.—I. W., a white widowed housewife aged 73, acquired severe pruritus over the sacral area in September 1947 and soon afterwards noted a group of small "blisters" in the same region. The eruption spread peripherally, and within a short time a vesicular eruption appeared on the arms, thorax, legs and back. The pruritus was intense, and even slight scratching seemed to be followed by new vesicles and bullae. The scalp exhibited a few vesicles, and finally the mucous membrane of the mouth was involved with vesicular lesions. New lesions appeared in successive crops, and the itching and burning became almost intolerable. The patient was first seen in the Department of Dermatology of University Hospital on Jan. 23, 1948, and admitted for treatment.

Physical examination revealed a well developed, obese elderly white female who appeared to be chronically ill and, because of a widespread crippling arthropathy, was unable to move about in bed. The scalp was not involved, and the face was also clear. There was one intact vesicle about the size of a pea on the right buccal mucosa. There were numerous large unilocular, thin-walled flaccid bullae, varying in size up to 1 cm. in diameter, on the thorax, abdomen, forearms and arms, posterior aspects of the thighs and sacral region. Most of the lesions exhibited an erythematous halo, while several bullae appeared to arise from perfectly normal skin. Numerous excoriations were visible throughout all involved areas. All the extremities showed the effects of a long-standing rheumatoid arthritic process. Aside from these observations, the physical examination revealed no abnormality.

The results of the admission urinalysis were normal. Blood studies showed 11.5 Gm. (80 per cent) of hemoglobin, 3,500,000 erythrocytes and 9,500 to 10,400 leukocytes, with eosinophil counts of 15, 10 and 44 per cent on three separate examinations. Fluid from a bullous lesion showed numerous eosinophils.

Treatment was started with coal tar solution (liquor carbonis detergens) baths, local application of an antipruritic ointment, sedation and oral medication consisting of four doses daily of 1 Gm. of sulfapyridine and 50 mg. of tripelennamine hydrochloride. The patient showed slow but progressive improvement on this regimen. The pruritus was of variable severity, being intense at times and minimal at others. Treatment was tolerated very well until the ninth day, when the patient manifested a blotchy erythema of the face and a generalized maculopapular and erythematous eruption which necessitated discontinuance of administration of sulfapyridine. On Feb. 3, 1948, the patient was started on treatment with 20 cc. of a 10 per cent solution of sodium paraaminobenzoate every three hours throughout the day and night, in addition to the local therapy. There was almost immediate relief from the pruritus, and the skin cleared promptly. The patient was discharged from the hospital on Feb. 8, 1948, with instructions to take 3 Gm. of sodium paraaminobenzoate seven times daily and to return after two weeks for further evaluation. By February 21 the patient's eruption had subsided com-

pletely though she still complained of pruritus. Because the condition had improved, however, the patient largely omitted further medication and had begun to manifest new lesions by March 19. She was advised to resume adequate doses of paraaminobenzoic acid to control her disorder but failed to do so.

CASE 4.[6]—S. H., a white factory worker 42 years of age, was first seen on Feb. 21, 1948, complaining of a pruritic vesicular eruption involving the sacral area, trunk, neck, ears, axillas, scrotum and legs, of one year's duration. Local medications had afforded no relief, and no response was noted when the administration of 100 mg. of diphenhydramine hydrochloride, three times daily, was combined with local therapy. The use of sulfapyridine, 1 Gm. four times daily, produced prompt improvement, but the drug had to be discontinued after 10 days because of nausea, vomiting and a drop in the hemoglobin level from 88 to 60 per cent.

On April 3, 1948, the patient presented many patches of grouped vesicles, along with excoriations, hyperpigmentation and scarring over the previously involved skin areas. Pruritus was intense. The patient was started on treatment with sodium paraaminobenzoate, 2 Gm. every two hours during the day and every four hours (two doses) during the night. Five days later the pruritus was much relieved and there were fewer lesions, with only an occasional new vesicle appearing. After 19 days of therapy, all vesicles had disappeared and there was only an occasional pruritic papule on the neck. The medication was discontinued for one week without recurrence of vesicles and was then resumed and continued until May 13, 1948. An occasional mildly pruritic papule appeared during this time. Leukocyte counts and hemoglobin on May 13 were 5,000 and 80 per cent, respectively.

Thirteen days after discontinuance of the medication, there was a reappearance of pruritic vesicles. Treatment with triple combisul® (containing equal parts of sulfadiazine, sulfathiazole and sulfamerazine) 0.5 Gm. four times daily, was started on June 5, 1948. At that time the patient had 9,450 white blood cells, 89 per cent hemoglobin and 5,100,000 red blood cells. The eruption gradually cleared, and no new lesions appeared while the patient was taking 0.5 Gm. of combisul® three times daily. Results of urinalyses and blood counts remained within normal limits.

CASE 5.—L. B., a 62 year old white man employed as an attendant in a mental hospital, was first seen in the University Hospital on June 11, 1948, complaining of a pruritic and burning eruption of six years' duration. This involved the trunk, arms, axillas, thighs and inguinal regions and the external genitalia. The original outbreak had consisted of grouped vesicles on the lateral and anterior aspects of the trunk with lesser involvement of the proximal extremities. There were remissions and exacerbations for the first three years, but in the past three years prior to the patient's being seen here there had been bullous lesions present on the body continuously. Treatment with ultraviolet and roentgen radiation, carbarsone, intramuscular injections of bismuth salts and penicillin and numerous lotions and ointments had been ineffective.

The physical examination revealed no abnormality except for the skin observations. There was a symmetrical patchy, bullous eruption involving the trunk, arms, thighs, external genitalia, axillas and inguinal regions, showing definite grouping and, in places, coalescence of lesions. Various stages of evolution were present, including intact, tense bullae, denuded erythematous patches, crusts, flaccid ruptured lesions and residual hyperpigmentation.

The reaction to the Kahn test was negative. Results of blood examinations were within normal limits. Urinalyses revealed a number of pus cells and motile Trichomonas vaginalis organisms. Roentgenologic examination of the chest revealed no abnormality. A skin biopsy showed changes compatible with chronic dermatitis which could not be specifically diagnosed.

The patient was placed on a reducing diet because of his obesity (admission weight was 209 pounds [95 Kg.]); neocalamine liniment was applied locally, and on June 15, 1948, treatment was started with 2 Gm. of paraaminobenzoic acid given by mouth every three hours, night and day. The patient tolerated the medication very well and after three days was very much encouraged. The amount of paraaminobenzoic acid was increased to 3 Gm. every three hours. There was pronounced symptomatic and clinical improvement noted within four days, and the patient was discharged from the hospital on a treatment schedule of 3 Gm. of paraaminobenzoic acid to be given seven times daily. He was seen again on June 30, 1948. There were only a few vesicles

6. Dr. Betty B. Owens, Middletown, Ohio, provided this case report.

and bullae present, and most of the old lesions had subsided. There were patches of erythema and dry scale where the bullous lesions had been present, along with hyperpigmented patches. The patient's chief complaints were dryness and tenderness of the skin and difficulty in sleeping at night. He had not followed instructions concerning the reducing diet. He was given nivea® oil (containing an emulsion of neutral aliphatic hydrocarbons in water with wool fat cholesterols) containing 1 per cent salicylic acid for local therapy, and the dosage of paraaminobenzoic acid was increased to 4 Gm. seven times daily.

The patient was next seen on July 19, 1948. He had numerous small vesicles in previously uninvolved areas, but there were fewer crusted lesions than there had been on his previous visit. He was seen again on Aug. 23, 1948, at which time he stated he had been almost completely free of lesions and symptoms one week previously and had voluntarily reduced the dosage of paraaminobenzoic acid to 2 Gm. every three hours. A few new vesicles had appeared in the previously involved areas. Aside from this manifestation only residual pigmentation remained. There were no subjective symptoms. Paraaminobenzoic acid therapy was discontinued entirely to see whether further exacerbation would occur. It was later learned that the expected pronounced flare-up of lesions did appear and the patient sought therapy elsewhere.

Case 6.—B. S., a 46 year old white housewife, was first seen at the University Hospital Dermatology Clinic on Sept. 24, 1948. She had experienced the onset of dermatitis herpetiformis in May 1948. Examination revealed characteristic lesions on the scalp, ears and the V of the neck, under the breasts and about the shoulders, elbows, the sacral area, the knees and the pretibial areas. There was slight hyperpigmentation in the involved areas. The patient received a course of 3 Gm. daily of sulfadiazine and 300 mg. of tripelennamine hydrochloride. During one month of treatment on this program, new lesions continued to appear and there was no improvement. Treatment was changed to the administration of asiatic pills, one three times daily, and this was continued for five weeks without benefit. On Dec. 4, 1948, the patient was started on paraaminobenzoic acid therapy, 21 Gm. daily. There was considerable relief by December 13, with only slight residual activity about the V of the neck. The total daily dose was decreased to 18 Gm. because of nausea. By December 30 the lesions had all cleared with complete relief of symptoms and the patient was tolerating the drug without nausea. She continued on the medication for three more weeks and then stopped because her supply of paraaminobenzoic acid was exhausted. She had remained clear of lesions but began to have a relapse within two weeks after the administration of paraaminobenzoic acid was discontinued. The relapse was in progress when the patient was seen again, on Feb. 4, 1949. She was given a three weeks' supply of paraaminobenzoic acid and advised to resume therapy of 18 Gm. daily. The exacerbation of lesions continued for a few days, and then there was gradual clearing. By the time the supply of paraaminobenzoic acid was finished the patient was clear of lesions, and she did not return for more of the drug. As a result the dermatitis herpetiformis lesions reappeared. The patient returned on March 18, 1949; although she had twice had clearing on paraaminobenzoic acid therapy, she did not wish to resume this form of therapy because it only suppressed her disorder and did not cure it.

Case 7.—R. B., a 67 year old white male, was admitted to the Dermatology Service on Sept. 3, 1948, complaining of sores and blisters over his entire body. He had been well until one year before admission, at which time lesions had appeared about the ankles. They resembled "mosquito bites" at first, were pruritic and within a few hours became bullous. The eruption persisted, with new lesions continually appearing while older ones seemed to heal. Gradually the skin over other parts of the body became similarly involved. The eruption had been generalized for at least four months prior to admission.

Examination revealed many bullous lesions from 0.5 to 3.0 cm. in diameter on all parts of the skin. In addition, there were many crusts and areas of hyperpigmentation in sites which had previously presented bullae. There were no mucous membrane lesions. The remainder of the physical examination was noncontributory.

Routine urinalysis yielded normal observations. The admission blood examination revealed normal hemoglobin and erythrocyte values. The leukocytes numbered 12,320 per cubic millimeter, with 84 per cent neutrophils, 4 per cent eosinophils and 12 per cent lymphocytes. The Kahn test on the blood serum gave a negative reaction.

The clinical diagnosis was either dermatitis herpetiformis or pemphigus vulgaris. The patient had a stormy hospital course characterized by fever, weight loss, progressive anemia and

continued development of bullae. Extensive hematuria appeared at one time and was associated with a prolonged clotting time which was not explicable by any known primary hematological disorder. Numerous subcutaneous hematomas also appeared at that time. In addition to a variety of local applications, the patient was treated with crysticillin® (procaine penicillin G for aqueous injection), 300,000 units given intramuscularly daily; dihydrotachysterol, and vitamin E. He also received numerous blood transfusions. By January 1949, the patient's condition had become worse and it was decided to treat him with potassium paraaminobenzoate. His general appearance on January 25 is shown in figure 4 *A*. Biopsy was made of a typical lesion on the skin of the abdomen and interpreted by the pathologist as a "classic example of dermatitis herpetiformis" (fig. 5).

Beginning on January 25 the patient received 3 Gm. of potassium paraaminobenzoate every three hours, day and night. Within three weeks there was considerable symptomatic improvement

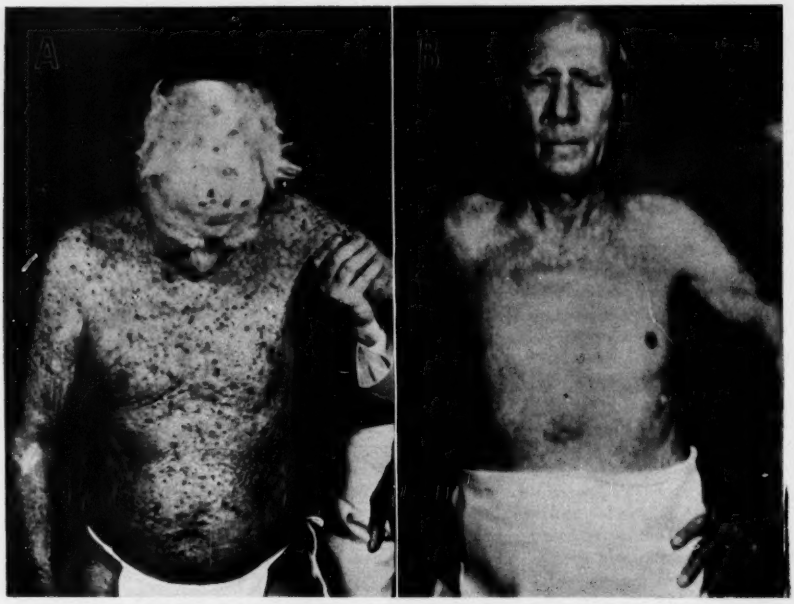

Fig. 4.—*A*, appearance of the patient in case 7 on Jan. 25, 1949, before starting paraaminobenzoic acid treatment. *B*, same patient on June 21, 1949, after almost five months of therapy.

but new small vesicles still appeared. Gradually the patient gained strength, the denuded areas healed and new lesions were no longer observed. By April 6, 1949, the improvement had been remarkable and the patient was discharged to continue therapy at home. He was instructed to take 18 Gm. of potassium paraaminobenzoate daily. On April 19 some crusts on the scalp were treated with an application of 10 per cent ammoniated mercury ointment. This therapy was followed in a few days by an acute local reaction with edema and erythema of the scalp and face. Weakness and lethargy were pronounced. The patient was readmitted, and the reaction gradually subsided under treatment. The administration of potassium paraaminobenzoate was interrupted only for two days and then resumed at the same schedule. Improvement continued, as can be seen in the photograph taken on June 21, 1949 (fig. 4 *B*). In addition to having the cutaneous improvement the patient gained weight and strength, his blood values gradually returned toward normal and the bizarre bleeding phenomena disappeared. On Oct. 25, 1949, another skin biopsy was taken from the site adjacent to that of the pretreatment biopsy specimen.

Fig. 5.—Photomicrograph of biopsy specimen of typical lesion from case 7, Jan. 25, 1949.

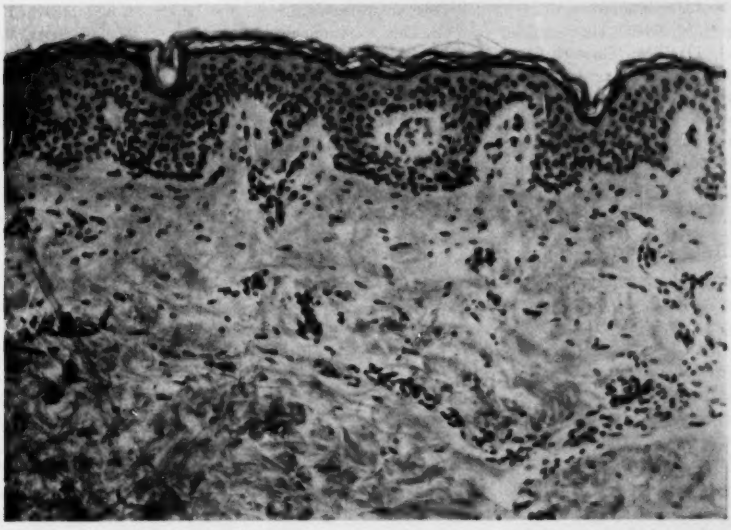

Fig. 6.—Photomicrograph of biopsy specimen taken Oct. 25, 1949, after nine months of treatment, from site adjacent to that shown in figure 5.

The pathologist noted only a slight degree of hyperkeratosis and a minimal amount of lymphocytic infiltration in the dermis. It was stated that on this material, in contrast to the other material from this case, a diagnosis of dermatitis herpetiformis or other specific skin change could no longer be made. A photomicrograph of a section of this specimen is shown in figure 6.

Therapy with potassium paraaminobenzoate was discontinued on Nov. 1, 1949, and the patient advised to return in the event of a relapse. As of June 1, 1950, he had not yet returned.

CASE 8.—W. L., a 56 year old white male, acquired a pruritic eruption in November 1948. He sought medical attention, and the diagnosis of herpes zoster was made. Later, as the process became more extensive, atypical lichen planus, dermatitis herpetiformis and lymphoblastoma were considered. Despite treatment with sulfapyridine, diphenhydramine and hydrochloride tripelennamine hydrochloride, the disorder progressed, and the patient was admitted to the University Hospital on Jan 27, 1949. Examination at that time revealed an extensive dermatitis over the shoulders, arms, thorax, abdomen and legs. The older-appearing lesions on the arms and shoulders consisted of excoriated papulosquamous erythematous areas. The lower legs showed many intact vesicles and bullae, as well as raw, exuding surfaces. There was 3 + pitting edema of the feet. There were no other pertinent physical observations.

Laboratory studies of the blood and urine yielded normal values except for a 21 per cent eosinophil count. Biopsy of a typical skin lesion on Jan. 31, 1949, was found to be compatible with a diagnosis of dermatitis herpetiformis.

Treatment was started with potassium paraaminobenzoate, 3 Gm. every three hours, making a total daily dose of 24 Gm. The lesions were also treated locally with potassium permanganate (1:20,000) baths and application of a 1 per cent solution of methylrosaniline chloride. While definite improvement occurred on this program, new lesions continued to appear. On March 5, 1949, it was decided to supplement the treatment with 4 Gm. of sulfapyridine daily. This therapy resulted in an acute exacerbation of generalized plaquelike lesions, pronounced pruritis and gastrointestinal discomfort. The administration of sulfapyridine was discontinued on March 7, leaving potassium paraaminobenzoate as the principal medication. Although there was considerable continued activity of the dermatitis herpetiformis, the patient was discharged on April 30, 1949. He remained on potassium paraaminobenzoate therapy, 21 Gm. daily, until Oct. 11, 1949. Throughout that period he experienced new, scattered lesions and associated pruritus. The process was thus only partially suppressed by paraaminobenzoic acid. It was therefore decided to stop paraaminobenzoic acid therapy, and asiatic pills, four a day, were administered. Within a few weeks the lesions had increased in number and size and pruritus was more intense. The patient returned for resumption of paraaminobenzoic acid therapy on Nov. 29, 1949. He had continued on treatment with 18 to 21 Gm. daily of potassium paraaminobenzoate through May 16, 1950, his most recent visit. The patient still experienced scattered pruritic papules on this program but preferred to take the potassium paraaminobenzoate for its partial effectiveness.

CASE 9.—M. B. B., a 29 year old white machinist, was first seen in the Department of Dermatology on April 28, 1949, at which time he complained of an extensive itching dermatitis. He gave a history of infantile eczema, with recurrences from time to time of an erythematous, papular, pruritic eruption, usually localized to the lateral aspects of the upper arms and shoulders. In May 1945, when the patient was stationed in the Marshall Islands, he had had an exacerbation of the eruption. He was treated for scabies, without improvement. After his discharge from the Navy in 1946 there was some improvement, but at no time was he free of lesions or pruritus. He managed a baseball team and noticed that ill fortunes of the team were reflected by exacerbations of his dermatosis. Treatment had included the use of numerous lotions and ointments, including the administration of sulfonamide preparations, to which he developed hypersensitivity. He had also received repeated courses of superficial roentgen irradiation to all lesions.

The physical examination revealed no abnormality except for the skin. A symmetrically distributed inflammatory, excoriated eruption was present on the shoulders, upper arms, back, buttocks, suprapubic region, lateral aspect of the thighs and popliteal spaces and consisted of patches of confluent papules and vesicles. Hyperpigmentation was present in the regions of involvement.

Results of laboratory examinations of the blood and urine were within normal limits. A skin biopsy taken from an area of papular lesions was not diagnostic. It revealed hyperplasia of the epidermis with some loss of differentiation in the basal layers. Subpapillary perivascular infiltrations were present and included leukocytes as well as lymphocytes.

The patient was started on treatment with a mixture of sodium and potassium paraaminobenzoate, 3 Gm. every three hours for six doses daily. During the first three days there was an increase in the severity of the pruritus, and then relief followed. At the end of a month, the patient was tolerating 18 Gm. daily and was almost completely relieved of itching. There was also pronounced improvement in the appearance of the eruption, with no new lesions. Thereafter, the patient took his medication irregularly, often not taking any for days at a time. Omission of the drug usually occurred at the time of trips with his baseball team. Recurrence of pruritus and the appearance of new vesicles followed lapses in medication. Because the patient failed to maintain a regular schedule of paraaminobenzoic acid therapy, other methods of treatment were begun on Sept. 1, 1949.

CASE 10.—M. S., a married white 37 year old plant engineer, was first seen in the Dermatology Department on June 2, 1949, complaining of a generalized skin eruption which had been present intermittently for 15 years. The dermatosis had been of only minimal severity during the first 12 years, and he had not sought the advice of a physician. For three years prior to his initial visit to the University Hospital, the eruption was characterized by episodes of remission and exacerbation, and in the last year the patient had had particularly severe episodes of the disorder. He had taken sulfapyridine with noticeable improvement for a time but had had to discontinue this drug because of toxic manifestations. Antihistamine preparations, combined with a different sulfonamide, were used for approximately six months, with some relief, but, because of undesirable side effects of the antihistamine drugs, these also had to be discontinued.

Physical examination revealed normal conditions except for the skin. Scattered over the trunk, shoulders and thighs and in the axillas and inguinal regions were patches of grouped papules and vesicles. Some of the vesicles were clear and tense and surrounded by a bright erythematous halo; others were excoriated, showing smooth red surfaces or crusted tops. There were areas of hyperpigmentation in which scarring could be seen. Only minimal regional lymphadenopathy could be made out.

The chest roentgenogram revealed no abnormality, and the Kahn test on the blood serum gave a negative reaction. Results of routine laboratory examinations of the blood and urine were within normal limits.

The patient was started on treatment with potassium paraaminobenzoate, 30 cc. of a 10 per cent solution every three hours for six doses daily. By July 1, 1949, the eruption on the back and abdomen showed evidence of regression while the axillary and inguinal patches appeared to have many vesicles which were secondarily infected. An antipruritic and drying lotion was prescribed for local use, along with baths, and the patient was advised to continue with the medication as previously outlined. The patient tolerated the paraaminobenzoic acid well, and treatment with this compound was maintained until Sept. 27, 1949. Although the eruption had subsided further, the process was not completely suppressed at any time. It was noted, however, that the new lesions were smaller and more transitory than those which had appeared prior to the paraaminobenzoic acid therapy. About 10 days after use of paraaminobenzoic acid had been discontinued there was an exacerbation of the eruption. The new lesions were larger and more extensive than those presented during the treatment with paraaminobenzoic acid. Because paraaminobenzoic acid had given only partial suppression of the dermatitis herpetiformis in this patient other forms of therapy were tried. These included the administration of chloramphenicol, 3 Gm. daily, and, later, ascorbic acid, 2 Gm. daily. Neither of these substances succeeded in controlling the process.

CASE 11.—D. J. O., a 66 year old white physician, was admitted to the University Hospital on Nov. 3, 1949. He had noted the onset of dermatitis herpetiformis lesions over the sacral area and buttocks eight months earlier. The eruption rapidly appeared on other parts of the body. He consulted a colleague who prescribed sulfapyridine, 3.0 Gm. daily. On this medication pronounced improvement was observed within three days. Within a few more days, however,

acute urinary suppression developed. The patient was admitted to another hospital in shock. He was placed in an oxygen tent because of cyanosis. Plasma and glucose were given intravenously. Albuminuria and hematuria were present at that time and persisted. The patient was discharged after three weeks of hospitalization. The dermatitis herpetiformis had recurred with its previous intensity, however, and was not influenced by courses of penicillin and aureomycin. On Nov. 5, 1949, potassium paraaminobenzoate therapy was begun. At first the patient received only 12 Gm. daily, but the daily dose was increased to 18 Gm. on December 8. The patient tolerated the medication well but had only partial relief from pruritus, and the eruption was not suppressed completely by the potassium paraaminobenzoate. He continued on this program until early April 1950, when he had an attack of diarrhea with associated nausea and anorexia. Within a few days the pruritus increased in severity and many new lesions appeared. The patient then placed himself on treatment with orally administered streptomycin, 0.5 Gm. daily for two weeks, without influencing his disorder. He was readmitted on May 2, 1950, for trial of other modes of therapy.

CASE 12.—D. W., a 28 year old white male medical student, had been troubled with dermatitis herpetiformis for 15 years. There had been spontaneous remissions and exacerbations, independent of seasonal or climatic factors. There was, however, a definite relation of exacerbations to stress factors—for example during final examination periods. The characteristic lesions had been localized to the axillas and the popliteal spaces, in the inguinal region, over the sacrum and occasionally in the antecubital fossae. Past therapy had included superficial roentgen irradiation, which gave some relief. This form of treatment had been employed on 20 occasions, however, and its continued use was not deemed advisable. Asiatic pills were tried, without benefit. Sulfapyridine gave satisfactory control initially, but later trials were unsuccessful. Sulfadiazine and antihistaminic drugs were also administered, but their use did not result in improvement. The patient was begun on paraaminobenzoic acid therapy on Nov. 22, 1949. He received a total of 15 to 18 Gm. daily of potassium paraaminobenzoate and sodium paraaminobenzoate. The medication was well tolerated, and within two weeks most of the lesions had cleared and the pruritus had subsided. The patient remained on this program and was observed periodically through May 23, 1950, his most recent visit. The disorder was suppressed satisfactorily, and the patient was more comfortable than at any time in recent years. A slight, transitory activity was occasionally evident, especially during periods of stress. This was not considered sufficiently troublesome, however, to warrant higher doses of paraaminobenzoic acid, and the patient continued to take 15 to 18 Gm. daily.

CASE 13.—L. D. W., a 31 year old white man, first acquired some intensely pruritic red papules on the buttocks in March 1948. The lesions gradually spread to involve the knees and the arms. The patient was first treated for scabies, without relief. In June and July 1948 he received arsenical medication, which is said to have made him worse. In the fall of 1948 he was started on treatment with sulfapyridine, 1 Gm. four times daily. He obtained prompt relief from the pruritus, and the lesions rapidly healed. The administration of sulfapyridine was continued for about one year, and then it was noted that both the red and white blood cell counts had fallen. The use of sulfapyridine was stopped, and the lesions and pruritus promptly returned. After the blood values had become normal, small doses of sulfapyridine were begun again. Although the pruritus disappeared the adverse effect on the blood elements was again observed. Treatment was discontinued, with a return of pruritus and lesions. The patient was admitted to the University Hospital on Nov. 24, 1949, for therapy.

Examination revealed numerous vesicles and excoriations over the arms, back, abdomen, perineum, thighs and knees. Patchy hyperpigmentation was present in the involved regions.

Routine urinalysis revealed no abnormality. The hemoglobin was 8.5 Gm. per 100 cc., and the leukocytes, 2,550 per cubic millimeter. The white cell differential count was within normal limits. Biopsy of one of the characteristic skin lesions revealed moderate acanthosis with subepidermal vesicle formation. The vesicle contained abundant eosinophils, as did the moderate inflammatory infiltration in the subpapillary layer of the dermis. The pathologist interpreted these observations as compatible with the clinical diagnosis of dermatitis herpetiformis.

The patient was given coal tar solution baths twice daily. He also received 50 mg. of diphenhydramine hydrochloride and 250 mg. of aureomycin four times daily. Although there

was some relief of pruritus after a week of this treatment, it was deemed advisable to change to potassium paraaminobenzoate therapy on Dec. 1, 1949. The patient was given 21 Gm. daily in seven doses of 3 Gm. each. There was an exacerbation of lesions for a few days, but within two weeks almost all signs of activity had disappeared. The patient returned to work and continued to take the same amount of potassium paraaminobenzoate. As of June 9, 1950, the process had remained suppressed except for an occasional scattered papule and the patient was comfortable. The hemoglobin value was 12.6 Gm. per 100 cc., and the leukocytes, 5,000 per cubic millimeter.

CASE 14.—C. E. S., a 42 year old white factory worker, was referred for paraaminobenzoic acid therapy on Dec. 27, 1949. He had had dermatitis herpetiformis for 11 years with characteristic exacerbations and remissions during that time. Previous treatment had included various local applications, roentgen irradiation and the administration of sulfapyridine. He had obtained some relief from these forms of therapy but stated that he had not been completely clear of lesions at any time since the onset of the disorder.

Examination revealed typical grouped lesions and hyperpigmentation in the antecubital fossae, in the perianal region, about the buttocks and also in the popliteal spaces. Scattered lesions were present in the scalp and over the thorax and abdomen. Pruritus was said to be severe and distressing. Routine examinations of the blood and urine revealed no abnormality.

Beginning on Dec. 27, 1949, the patient received 18 Gm. daily of a 50 per cent mixture of potassium paraaminobenzoate and sodium paraaminobenzoate. Within 10 days the pruritus had subsided and the skin lesions had almost all disappeared. The patient remained on paraaminobenzoic acid therapy with the same dosage through March 13, 1950. Except for a slight transitory "break-through" of activity in the left antecubital fossa the patient had remained more comfortable and with fewer lesions than at any time in years. He was advised to continue therapy for three more weeks and then to stop the use of paraaminobenzoic acid. He was asked to return in the event that lesions reappeared, but he had not done so up to the time of the present writing.

CASE 15.—L. M., a 32 year old white housewife, had had her first episode of dermatitis herpetiformis at the age of 17. Remissions and recurrences were noted during the ensuing years. She had two children, one aged 9 and the other 3. During each of her pregnancies the patient had been clear of all lesions, and she had remained so for several months after delivery. Her present relapse of dermatitis herpetiformis had begun in July 1949. There was a gradual progression of lesions so that by September there was involvement of the face, neck, upper arms, antecubital fossae, shoulders, axillas, back, inner aspects of the thighs and lower legs. Pruritus was intense. Despite superficial roentgen irradiation and other forms of therapy the lesions persisted, and the patient was admitted to University Hospital on Jan. 23, 1950. Examination confirmed the diagnosis, and the distribution of lesions was as given above. The patient was begun on potassium paraaminobenzoate therapy on Jan. 25, 1950, and discharged on January 30 to continue on treatment with 18 Gm. daily of this compound. Within two weeks the patient was clear of lesions. She remained on the same program until March 20, 1950, at which time treatment was discontinued because of the advent of anorexia and nausea. The patient's disorder had been suppressed throughout the period of paraaminobenzoic acid administration and had not recurred when the patient was last seen, on April 5, 1950.

CASE 16.—E. S., a 31 year old Negro man, was admitted to the Dermatology Service on Nov. 14, 1949. He had acquired a pruritic papular eruption 14 months earlier. The first lesions appeared on the chest, but gradually the flanks, back, arms and legs also became involved. Pruritus was intense, particularly at night. The patient had experienced little relief from the time of onset of the disorder.

Examination revealed a generalized papular eruption over most of the body. The lesions were more concentrated at the flanks, on the lower part of the back and on the extremities. Excoriations were numerous in the involved areas. The physical observations were otherwise normal.

Laboratory studies revealed normal blood and urine values. The chest roentgenogram on admission revealed no abnormality, and the reaction to the Kahn test on the blood serum was negative.

Treatment initially consisted in coal tar solution baths twice daily and the administration of aureomycin, 500 mg., five times daily and of 50 mg. of diphenhydramine hydrochloride three times daily. There was prompt improvement in the degree of pruritus, and the patient was discharged on November 19 to continue the aureomycin therapy at home. He returned on November 29 complaining of severe sore throat. Examination revealed acute pharyngitis. The tongue and buccal mucous membranes were also inflamed and sore. Agranulocytic angina was considered, but the patient's leukocyte count was normal in all respects. Treatment with aureomycin was discontinued, and sulfadiazine was prescribed, 1 Gm. every four hours for five days. The sore throat promptly subsided. Two weeks later there was still much activity of the dermatitis herpetiformis. The patient was then given sulfapyridine, 1 Gm. four times daily, from Dec. 12, 1949, to Feb. 3, 1950. During that period there was little relief from the pruritus and the eruption seemed to increase. Administration of sulfapyridine was stopped and doxylamine succinate (decapryn®) given. On February 16 the patient had a tonsillectomy, and he resumed treatment with doxylamine succinate shortly afterward. This therapy also failed to control either the eruption or the pruritus. Potassium paraaminobenzoate therapy was therefore begun on March 22, 1950. The patient received 18 Gm. daily of this compound until May 17. Concomitantly there was almost complete subsidence of the process, with no new lesions and only occasional pruritus. Although the dermatitis herpetiformis was satisfactorily suppressed, the patient had noted the occurrence of an urticarial dermatitis within a few minutes after his ingestion of wheat products. His present program is directed toward the control of the allergic phenomena, after which more definite evaluation of therapy for the dermatitis herpetiformis should be possible.

COMMENTS

Dermatitis herpetiformis is characterized by spontaneous remissions and exacerbations. From the foregoing case reports, however, it is evident that the administration of large doses of paraaminobenzoic acid has been followed by partial to complete suppression of the disorder in all 16 patients. The improvement required 18 to 24 Gm. daily of potassium paraaminobenzoate or sodium paraaminobenzoate, although continued control was sometimes achieved on lower doses. In general, paraaminobenzoic acid not only suppressed the appearance of new lesions but also caused the pruritus to subside. It usually required two to three weeks of therapy to achieve this effect. As control of the process was maintained over longer intervals there was gradual fading of hyperpigmented areas. Relapse began to appear about 10 days after the cessation of treatment. After reinstitution of therapy two to three weeks were required for suppression of the disorder to be regained. Furthermore, it was not unusual to observe a continued exacerbation of lesions during the first few days of renewed treatment.

After it had been noted that relapse usually did not appear until some 10 days after discontinuation of therapy, it was decided to attempt intermittent treatment with paraaminobenzoic acid. Thus, treatment was stopped in a patient whose disease was under control. Five days later, he was still clear of lesions and administration of paraaminobenzoic acid was resumed. A few days later, however, pruritus and new lesions appeared. While these subsided during continued administration of paraaminobenzoic acid, it was evident that intermittent therapy would not give adequate control of the disorder.

Some of the patients gradually reduced the daily intake of paraaminobenzoic acid from the initial 18 to 24 Gm. to 12 to 15 Gm. On this program satisfactory suppression of the disease was achieved. Although there appeared occasionally

an isolated pruritic papule, it was considered less troublesome to have such a lesion than to take the higher amount of paraaminobenzoic acid.

It should be emphasized that almost all these patients had previously received other forms of therapy for dermatitis herpetiformis. Several were resistant to the usual treatments. Furthermore, sulfapyridine therapy had given rise to toxic manifestations in about half of this group. Reactions had ranged from nausea and vomiting to hemolysis and acute renal suppression. Thus, paraaminobenzoic acid was the only satisfactory therapy for several patients. It is of interest that treatment with this compound was maintained for as long as 30 months without the encountering of any serious toxicity. Nausea, occasionally associated with vomiting, was the main untoward effect. This usually subsided on the omission of the drug for a day or so, whereupon treatment with it could be resumed, often without further difficulty. In this connection, experience indicates that potassium paraaminobenzoate is better tolerated than the sodium salt. Some of the patients preferred a 50 per cent mixture of the two salts.

While other toxic reactions have been noted during paraaminobenzoic acid therapy, they were not observed in these patients. Drug fever has been described but has been almost always observed in lupus erythematosus patients receiving the compound.[7] Repeated leukocyte studies failed to reveal any cases of agranulocytosis, but the practice of periodic checking of the blood should not be discarded unless further study permits it.

The principal complication which may arise during the administration of paraaminobenzoic acid is spontaneous hypoglycemia.[8] This did not occur in any of this group of cases but has been observed in patients who are continued on treatment with the drug while nauseated and unable to maintain a normal dietary intake. The mechanism by which hypoglycemia occurs is under study at present. It should be emphasized, however, that treatment for this situation is the same as for acute hypoglycemia due to any cause. In general, this complication may be avoided by instructing the patient to eat well while taking paraaminobenzoic acid. If anorexia or nausea occur, use of the drug is to be omitted until the patient is again eating normally.

The mode of action of paraaminobenzoic acid in dermatitis herpetiformis is unknown. It is of interest that paraaminobenzoic acid, sulfapyridine [9] and nicotinic acid,[10] compounds with structural similarities chemically, are all capable of suppressing the activity of dermatitis herpetiformis. One patient in this series received paraaminobenzoic acid and sulfapyridine concurrently and became worse when the sulfonamide was added to his treatment. This development may have been the result of hypersensitivity to the sulfonamide compound rather than paraaminobenzoic acid antagonism. It should be noted in this connection, however, that Costello [9] observed a similar result when the substances were administered in reverse order.

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7. Footnote 2. Zarafonetis, Grekin and Curtis.[3e]

8. Zarafonetis, C. J. D., and Chandler, J. P.: To be published.

9. Costello, M. J.: Sulfapyridine in the Treatment of Dermatitis Herpetiformis, Arch. Dermat. & Syph. **56**:614-628 (Nov.) 1947.

10. Johnson, H. H., Jr., and Binkley, G. W.: Nicotinic Acid Therapy of Dermatitis Herpetiformis, J. Invest. Dermat. **14**:233-238, 1950.

It seems evident from this and other studies that additional investigation of the more fundamental aspects of the physiological effects of paraaminobenzoic acid are highly desirable. From a practical standpoint, moreover, it appears that paraaminobenzoic acid may be a useful adjunct in the management of selected cases of dermatitis herpetiformis.

SUMMARY

Sixteen patients with dermatitis herpetiformis were treated with large doses of potassium and/or sodium paraaminobenzoate. All experienced partial to complete suppression of the disorder while taking the compound. Relapse usually occurred about 10 days after cessation of therapy. Remissions were maintained, however, through continued administration of the drug, for as long as 30 months.

Clinical Notes

CUTANEOUS HYPERSENSITIVITY TO TEAR GAS (CHLOROACETOPHENONE)

A Case Report

JOHN F. MADDEN, M.D.
ST. PAUL

Kissin and Mazer [1] stated that large numbers of soldiers were exposed to tear gas during training against chemical attack and that, though a few instances of cutaneous hypersensitivity to tear gas were reported [2] at their station, among more than 10,000 individual exposures to chloroacetophenone only one resulted in a significant reaction. A War Department technical manual [3] noted that tear gas may cause immediate cutaneous burning and erythema when the environmental temperature is high and the skin is moist.

In Kissin and Mazer's patient there was no skin reaction after the first exposure, a mild dermatitis appeared on the hands and trunk within 30 hours and lasted four days after the second exposure and a severe generalized dermatitis exempting the face appeared within 10 hours and lasted 10 days after the third exposure. Patch tests gave strongly positive reactions and produced a flare of the original generalized dermatitis.

Ingram [2b] and Queen and Stander [2a] each recorded an additional case in soldiers. Contact dermatitis from tear gas appears to be very rare among soldiers who are in frequent contact with the gas during certain types of training; therefore it was thought that contact dermatitis from tear gas in a civilian would be of medical interest.

REPORT OF CASE

A civilian law enforcement officer was seen in July 1938 with a mild erythematous dermatitis involving the legs. He was given an antipruritic lotion and colloidal baths. The eruption involuted in about a week. The patient was seen again in May, June and August 1943 with a similar but severer contact dermatitis on the legs. The duration was longer with each attack. The eruption occurring in August took three weeks to heal and extended to the thighs. It was thought that the patient had a weed dermatitis, probably from poison ivy, because each recurrence appeared after week ends spent cleaning brush and working on country property which he had purchased. The patient usually wore shorts while doing this work. In July 1945 he returned with the most severe recurrence extending over both legs. At this time the patient also made the diagnosis. His office received "dated" tear gas bombs from a central source. After the expiration date on the bombs the officers were ordered to destroy them and procure new ones. The patient decided to use the old bombs to try to eradicate the rodents which were tunneling and damaging his property. He would discharge the tear gas into the entrances of the various subterranean channels and stand by waiting for some-

From the Department of Dermatology and Syphilology, Ancker Hospital, St. Paul, Dr. John F. Madden, director, and the Division of Dermatology and Syphilology, University of Minnesota, Dr. H. E. Michelson, director.

1. Kissin, M., and Mazer, M.: Cutaneous Hypersensitivity to Tear Gas (Chloroacetophenone). Bull. U. S. Army M. Dept., October 1944, no. 81, pp. 120-121.

2. (*a*) Queen, F. B., and Stander, T.: Allergic Dermatitis Following Exposure to Tear Gas (Chloroacetophenone, CN) J. A. M. A. **117**:1879 (Nov. 29) 1941. (*b*) Ingram, J. T.: Dermatitis from Exposure to Tear Gas, Brit. J. Dermat. **54**: 319-321 (Dec.) 1942.

3. Treatment of Casualties from Chemical Agents, United States War Department, Technical Manual 8-285, Washington, D. C., Government Printing Office, Nov. 27, 1942, p. 21.

thing to happen. A recurrent contact dermatitis from tear gas resulted. A small area on one leg was directly exposed to tear gas after the last attack subsided; itching began at once, and an acute contact dermatitis appeared on the exposed area within eight hours. The patient has not had a recurrence since 1945.

SUMMARY

To the best of my knowledge, this is the first report of a case of recurrent contact dermatitis from tear gas in a civilian.

TREATMENT OF HERPES ZOSTER OPHTHALMICUS WITH AUREOMYCIN

WILLIAM A. ROSENBERG, M.D.
Assistant Professor of Dermatology and Syphilology, Chicago Medical School
CHICAGO

Zoster ophthalmicus may be a severe and dangerous manifestation of herpes zoster, often accompanied with agonizing pain and formidable involvement of various parts of the eye, and may result in panophthalmia, ulcerative keratitis, blindness, pyemia, meningitis and death.

The internal treatment of herpes zoster, as a rule, is directed toward relief of pain, and in severe cases complete protection of the part can be accomplished best by complete rest at home or in the hospital. Posterior pituitary (pituitrin®) [1] given intramuscularly every other day is of value in relieving pain; sodium iodide [2] given intravenously in 2 Gm. doses every other day has been successful in some cases; opiates may be administered hypodermically or orally, and recently aureomycin [3] has been effectively used. Local treatment is primarily directed toward protecting the part from infection and obtaining relief from burning and itching. Aluminum acetate solution 1:20 may be applied as a wet dressing; antiseptic ointments and cocaine ointment 1 per cent have been recommended. A solution of aureomycin may be applied locally.

Recently I had the opportunity of observing two cases of zoster ophthalmicus, in one of which the eyeball was implicated. These cases were treated effectively with aureomycin. Because there is no recent reference in the literature to such therapy this preliminary report is presented.

REPORT OF CASES

CASE 1.—Mrs. M. W., a white housewife 56 years old, was first seen five days after the onset of severe headache and pain about the left eye and forehead. At this time there were typical clusters of vesicles on an inflammatory edematous base, involving the eyelids, the left half of the forehead and the anterior part of the scalp, the eruption being sharply demarcated at the midline. There was extensive edema of the upper lid and less involvement of the lower lid, with almost complete closure of the eyelids. Ophthalmologic examination showed no extension of the process to the eyeball, and a 1 per cent solution of atropine was instilled into the eye. The patient was hospitalized on Nov. 12, 1949, and was given aureomycin, 250 mg. orally four times a day. Two days later, she reported pronounced relief from pain and the edema about the eyelids had practically subsided. The aureomycin therapy was continued until November 19, at which time the skin lesions had practically healed, leaving pigmented macules, some of which left permanent scars. Further observation showed no extension of the process to the

1. Sidlick, D. M.: The Use of Solution of Pituitary in Herpes Zoster, Arch. Dermat. & Syph. **22**:91 (July) 1930.

2. Ruggles, E. W.: Apparent Specific Effects of Sodium Iodide in Herpes Zoster: Preliminary Report, Arch. Dermat. & Syph. **23**:472 (March) 1931.

3. Binder, M. L., and Stubbs, L. E.: The Treatment of Herpes Zoster with Aureomycin, J. A. M. A. **141**:1050 (Dec. 10) 1949.

eyeball. The blood count revealed no pathologic changes; there was no albumin or sugar in the urine, and the Kahn reaction of the blood was negative.

CASE 2.—Miss F. W., 43 years old, was first seen 48 hours after the onset of severe pain about the left eye and in the back of the head. At this time there were typical clusters of vesicles on an erythematous base, involving the eyelids, left half of the forehead and anterior part of the scalp. There were moderate edema and redness of both eyelids. The following day grouped vesicles on an erythematous base occurred also on the left cheek and infraorbital region. Ophthalmologic examination at this time showed no extension of the process to the globe, and a 1 per cent solution of atropine was instilled into the eye. Six days after the onset the patient acquired an interstitial keratitis. On Nov. 17, 1949, she was hospitalized and given aureomycin, 250 mg. orally every four hours five times daily. A solution of aureomycin (25 mg. in 5 cc. of solvent) was instilled into the eye three times daily, and pledgets of cotton soaked in the solution were applied to the conjunctiva. The treatment was continued for five days, after which time there was pronounced improvement, the pain in the head ceased and the interstitial keratitis had practically healed. Further observation showed no complications or residue.

CONCLUSIONS

Two cases of herpes zoster ophthalmicus, one involving the eyeball, were successfully treated with aureomycin. In the past zoster ophthalmicus with extension of the process to the eyeball was resistant to all forms of therapy.

185 North Wabash Avenue.

AUREOMYCIN OINTMENT IN VERRUCAE PLANAE

SIDNEY J. ROSE, M.D.
BEVERLY HILLS, CALIF.

Verrucae planae are considered by most authorities to be due to a filtrable virus.[1] A clinical note on treatment of molluscum contagiosum with aureomycin by Guy and associates[2] prompted my use of this antibiotic in an extensive case of verrucae planae of the face in a young child.

The difficulty of handling an extensive case in children where cooperation is necessary in the painful procedures of solid carbon dioxide applications, curettage and application of trichloroacetic acid, for example, as reported in all dermatologic texts, makes a simple remedy, if efficacious, highly desirable.

D. U., aged 6, was seen with approximately 80 lesions of typical flat discrete verrucae of the face and a few scattered lesions on the dorsa of both hands, of one year's duration.

A 10 per cent solution of trichloroacetic acid was prescribed to be used at night in order to macerate superficially the keratin layer, and aureomycin ointment, to be applied in the mornings. Examination one week after the start of this regimen revealed that all traces of verrucae had gone with no residual scarring.

Obviously, one such case offers insufficient evidence for universal adoption of such a procedure, especially in a condition where spontaneous cures can occur.[3] The results, however, warrant clinical trial in order to evaluate further a simplified means of handling an otherwise difficult therapeutic problem.

360 North Bedford Drive.

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2. Guy, W. H.; Jacob, F. M., and Guy, W. B.: Aureomycin in Molluscum Contagiosum, Arch. Dermat. & Syph. **60**:629 (Oct.) 1949.

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USE OF ETHYL CHLORIDE IN MINOR DERMATOLOGIC SURGERY

ELMER R. GROSS, M.D.
and
CARROLL S. WRIGHT, M.D.
PHILADELPHIA

Because of a lack of necessary equipment, Dr. Irving Schonberg [1] first used ethyl chloride in the removal of servicemen's verrucae.

For the past year we have adopted a modification of his method and extended its use to the removal of verrucae, keratoses, fibromas, nevi to which it was applicable, skin tags and other benign growths.

Ethyl chloride is sprayed on the affected surgical site until a frost appears. The site develops a boardlike hardness, and then quickly small sharp scissors are employed to remove the surface of the lesion. On completion of this procedure the site of the growth attains its normal texture. Then curettage is employed when indicated, and the base of the lesion is lightly touched with 50 per cent trichloroacetic acid. The entire procedure takes about 15 seconds and is especially adaptable for children.

Caution should be taken not to employ electrosurgical methods when ethyl chloride is used because of the inflammability and combustibility of ethyl chloride in the gaseous state.

We have found this simplified technic uncumbrous, painless and expedient in the removal of benign cutaneous growths.

1402 Spruce Street (2).

1. Personal communication to the author.

REINFECTION IN EARLY SYPHILIS THAT HAD BEEN TREATED WITH PENICILLIN (PING-PONG SYPHILIS)

JOHN J. STEWART, M.D.
JOHN G. THOMSEN, M.D.
and
ROBERT K. GARDNER, M.D.
CLEVELAND

The following case report is presented as a striking example of reinfection in syphilis that had been treated with penicillin.

H. H., a Negro aged 25 years, was first seen by us on April 20, 1949, with a history of a penile sore of one week's duration. He named E. W., a patient found to be under treatment for early syphilis in our clinic, as his only contact; he denied that he had a wife. There was no history of previous lesions or treatment of syphilis. A serologic test had given negative reactions in 1946. Examination revealed an indurated papular lesion surrounding the external urinary meatus and firm, nontender enlarged inguinal lymph nodes bilaterally. Physical examination was otherwise noncontributory. Dark field examination of the lesion was positive for Treponema pallidum; the Wassermann reaction was 4+; the Kline reaction was 4+ in a quantitative dilution of 1:10 and 3+ in a dilution of 1:20; the spinal fluid was normal. The patient was given an initial injection of 0.06 Gm. of oxophenarsine (mapharsen® hydrochloride) and daily injections of 300,000 units of procaine penicillin G for 20 days (6,000,000 units total). When treatment

From the service of H. N. Cole, M.D., Department of Dermatology and Syphilology, University Hospitals, Western Reserve University School of Medicine.

was completed, on May 13, the Wassermann reaction was negative, the Kline reaction was negative in a dilution of 1:10, the Kline diagnostic test reaction was 2+, Kline exclusion test reaction was 3+, and the chancre was healed. One month later, on June 15, the serologic reactions were all completely negative and there remained no evidence of the lesion.

On June 21 the patient's wife appeared in the clinic with multiple indurated papules on the chin and face, cervical adenitis and a lesion on the fourchet which was dark field–positive for Treponema pallidum. The Wassermann reaction was 3+; the Kline reaction was 4+ in a quantitative dilution of 1:20 and 2+ in a dilution of 1:40; the spinal fluid was normal. This woman was given the same treatment as had been given her husband, treatment being completed on July 13, at which time the Wassermann reaction was negative and the Kline reaction 4+ in a dilution of 1:10. On August 23 the serologic reactions were completely negative, and they remained so through Nov. 15, 1949.

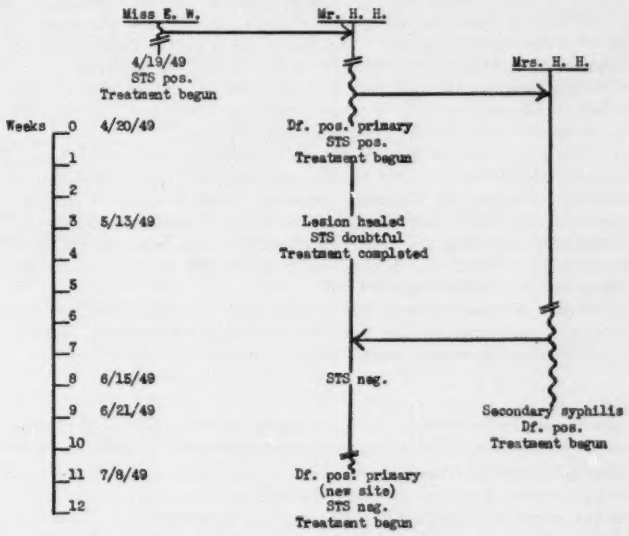

Chart showing course of infection. The arrows indicate transmission of infection; the wavy line, presence of infectious syphilis; the parallel cross bars, time in weeks; STS pos. and STS neg., positive and negative reactions, respectively, to the serologic test for syphilis, and df. pos., positive on dark field examination.

H. H. reappeared on July 8 complaining of a second penile lesion of three days' duration. He had resumed sexual relations with his wife on completion of his treatment on May 13, their last contact having been a few days prior to the beginning of her treatment on June 21 (12 days prior to this admission). There was a dime-sized, indurated, ulcerated lesion on the glans penis to the left of the meatus (a site different from that of the previous chancre); the remainder of the physical examination was noncontributory. Material from the lesion was found to contain Treponema pallidum on dark field examination. On this admission his serologic reaction was completely negative, as it had been the month before, and the spinal fluid was again found to be normal. He was re-treated in the exact fashion as with the first infection. The lesion healed promptly, and serologic reactions over a period of three months have remained negative.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

Maurice J. Costello, M.D., Chairman

Wilbert Sachs, M.D., Secretary

Oct. 4, 1949

Lymphogranuloma Venereum with Negative Reaction to Frei Test. Presented by DR. ORLANDO CANIZARES.

L. M., a Negro woman aged 27, was admitted to Bellevue Hospital on May 16, 1949, with elephantiasis and fibrosis of the vulva and open ulcerative granulomatous lesions of the natal cleft. She complained of pain on defecation. Review of admissions to Kings County Hospital indicated that she had been treated for lymphogranuloma venereum in 1942, 1943 and 1944 and that in 1945 a colostomy had been performed for rectal stricture. She was readmitted in 1948 with the same complaint and received sulfadiazine and estrogens.

In 1942 the reaction to the Frei test was reported as positive. A biopsy was also performed at this time and reported as "compatible with lymphogranuloma venereum." Clinical and laboratory studies at Bellevue Hospital revealed the following results: Frei and Ducrey reactions were consistently negative. The complement fixation test for lymphogranuloma venereum was negative in serum dilutions from 1:5 to 1:60. A biopsy on June 24, 1949, was reported as "granulomatous lesions, probably tuberculous."

Treatment since admission to Bellevue Hospital has consisted in the administration of streptomycin, 60 Gm., penicillin, aureomycin, sulfadiazine, transfusions and calciferol. The patient's condition has improved only moderately.

DISCUSSION

DR. MABEL G. SILVERBERG: It is interesting that the response to therapy has been poorer in this instance than in the average case with a positive Frei reaction.

DR. ORLANDO CANIZARES: I think it was Dr. Grace who reported cases of lymphogranuloma venereum in which the Frei reaction was positive and then, after the administration of sulfonamide drugs, became negative. Those were of the early inguinal type. My experience is that the late rectal type has first a negative and later a positive reaction. The fact that this patient has had repeated Frei tests would rule out the possibility of a weak antigen. I have had some cases in which there was a response to the intravenous test when the cutaneous Frei reaction was negative. We cannot perform the intravenous test any more because the mouse brain antigen is no longer available. This patient has responded fairly well in the last month or so to aureomycin, and I think that fact too is in favor of the diagnosis.

Tertiary Syphilis with Multiple Gummas of Skin and Bones Responding Poorly to Penicillin Therapy. Presented by DR. FRANK C. COMBES.

G. L., a Negro woman aged 41, was previously presented before the Manhattan Dermatological Society on March 8, 1949. On her first admission to Bellevue Hospital, in October 1948, she presented: (1) a gumma on the forehead, (2) nearly healed lesions with characteristic scarring on the anterior aspect of the left shoulder, (3) an active lesion on the right shoulder, (4) an extensive gummatous ulceration affecting the anterior and upper aspect of the left tibia and (5) gummatous osteomyelitis and periostitis of the skull, tibia. etc.

The serologic reactions have remained strongly positive. The Kahn quantitative reaction fell from 512 on discharge to 64 on January 31, when the patient was re-treated with 6,000,000 units of penicillin. On March 2 the titer was 16, but it thereafter rose and was 256 on September 15, when the patient was readmitted.

There was clinical improvement for the first few months after treatment, but during the last few the open lesions have been almost at a standstill, and recently there has been evidence of activity in the involved tibia. The patient is now receiving combined arsenobismuth therapy.

DISCUSSION

DR. LOUIS CHARGIN: I doubt whether on clinical grounds a diagnosis of gummas is justifiable. The ulcers lack the base and borders of true gummas. Failure to respond to antisyphilitic therapy must be attributed to that fact. If indeed they are gummas, there must be secondary changes present which prevent healing after the administration of penicillin, arsenic and bismuth preparations.

DR. LOUIS TULIPAN: I think this condition fits into the category that has been described as indolent syphilitic ulcers. I once wrote an article (*Urol. & Cutan. Rev.* **44**:541-542 [Aug.] 1940) on such ulcers and ascribed the difficulty in treatment to the fact that these ulcers have such a thick, fibrous wall, with obliteration of blood vessels, that they contribute to the stasis factor. I suggested that the border be destroyed by electrodesiccation and curettage plus the local application of mild mercurial ointment U. S. P. I was able to heal up these ulcers in a great majority of the cases.

DR. CHARLES WOLF: The clinical aspects lead one to believe the lesions are chronic gummas. Lack of response to penicillin is an example of drug-fast resistance. The fact that the patient did not respond to penicillin does not rule out syphilis. A desirable therapeutic measure would be the old-fashioned method of giving a bismuth preparation and potassium iodide. This is a case of penicillin-fast old gummatous, fibrous lesions.

DR. EMANUEL MUSKATBLIT: I wonder whether potassium iodide will have any effect on old fibrous connective tissue.

DR. ANTHONY C. CIPILLARO: There is evidently some difference of opinion as to whether the ulcers are of syphilitic nature. The woman has serologic evidence of syphilis. Before treating her further, I wonder whether it would not be wise to perform a biopsy, because neoplastic ulcers can imitate syphilitic and other lesions.

DR. MARION B. SULZBERGER: This woman has syphilis, and she has multiple torpid, gumma-like ulcers. Not only have these failed to heal but also the serologic titer has relapsed after large and generally adequate doses of penicillin. Is there penicillin-resistant syphilis, and, if so, what is the percentage of its occurrence? This summer, when I spoke to various heads of departments of dermatology and syphilology in France and Switzerland, one of the questions that came up constantly was, should one treat syphilis with penicillin alone? I followed the trails of Earl Moore and Evan Thomas through Europe, and most of the European dermatologists and syphilologists were not favorably inclined to treating the disease with penicillin alone. Practically all the French thought it better to use either combined or consecutive courses of penicillin and the older antisyphilitic drugs, such as bismuth compounds and even oxophenarsine hydrochloride (mapharsen®). I think we should consider these questions carefully and, if possible, decide whether this case may perhaps demonstrate the fact that, though rare, there can be such a thing as penicillin-resistant syphilis. Instead of using a procaine salt of penicillin, it seems to me more logical to use a bismuth salt, which is equally insoluble and which, according to Dr. Monash, gives off both bismuth and penicillin. If Dr. Monash's observations prove correct, it would seem useless and foolish to inject procaine, which has no antisyphilitic action and which may

sensitize or produce reactions in the patient, when one can accomplish the same slow dissociation and prolonged effect by injecting a preparation from which two valuable antisyphilitic remedies can be absorbed. Moreover, the iron salt "ferricillin," developed by W. Jadassohn and his group in Geneva would, in theory, appear also to possess advantages over procaine penicillin. American pharmaceutical houses doubtless have good reasons for passing over "bismucillin" and "ferricillin" and concentrating entirely on procaine pencillin, but I, for one, have never heard these reasons discussed nor seen them published.

DR. S. IRGANG: I have observed penicillin-resistant cases of early syphilis when this preparation was first employed, the dose having been adequate in each case. Regarding Dr. Sulzberger's suggestion of employing a preparation containing both penicillin and bismuth, I do not believe it would prove satisfactory. We have had an ineffective preparation of bismuth and arsphenamine in the form of bismuth arsphenamine sulfonate (bismarsen®). I think it preferable to administer each drug separately.

DR. LOUIS CHARGIN: I have not as yet encountered an active cutaneous manifestation of syphilis that has failed to respond to penicillin therapy. This is certainly true for early manifestations and also true in the few cases of late syphilis that I have treated. With respect to the remarks of Dr. Sulzberger, I have on a number of occasions expressed the view that penicillin alone is adequate for the cure of primary seronegative and seropositive syphilis but that secondary syphilis, for the best results, will require combined therapy with penicillin, arsenic and bismuth preparations.

DR. MAURICE J. COSTELLO: I recall a case of the late Dr. Astrachan's, of a man with massive destruction of the face as a result of long-standing syphilis, who was treated at several clinics in New York city with the various arsenicals. Dr. Astrachan decided to change the type of arsenic and administer dichlorophenarsine hydrochloride (clorarsen®), after which the process completely healed, leaving only the irreversible destruction of the tissues.

DR. FRANK C. COMBES: I agree with Dr. Chargin that the lesions should respond to penicillin; however, not only the lesions but also the titer in the Kahn quantitative test failed to respond, which fact I think is an indication of lack of response in this instance to penicillin rather than complete clinical failure. I have no idea why this patient has not shown response. It is possible that curettage may be of some benefit. The administration of a mercurial and potassium iodide may help. It may be that we are looking for too much from penicillin. It is extremely seldom that patients with syphilis do not respond to penicillin.

Squamous Cell Epithelioma Developing on an Old Granuloma Inguinale.
Presented by DR. FRANK C. COMBES.

J. T., a Negro aged 34, is presented from Bellevue Hospital. In 1937 the patient acquired an ulcer of the penis which gradually spread to involve the groin and scrotum. One graft was done but did not take. From 1938 to 1939 the patient was treated for syphilis, with no spread of the lesion but no improvement. He was re-treated in 1943. In March 1948 he was treated at Queens General Hospital with streptomycin and aureomycin with initial improvement which then stopped. He was admitted to Bellevue Hospital on April 20, 1949, presenting a massive ulceration 6 inches (15 cm.) in diameter involving the groin, penis and scrotum, with a nodular floor and an indurated, rolled border.

Biopsy from the center of the ulcer revealed a decidedly acanthotic epidermis with areas of ulceration at either end of the section. The epidermis showed pronounced thickening of the granular layer at regular intervals. The tumor deeply invaded the underlying connective tissue. Tumor cells were present in large sheets and took an eosinophilic stain. The cells varied considerably in size,

shape and staining power. No "pearl" formation was noted. The tumor was destructive and invasive. The histologic diagnosis was squamous cell carcinoma of relatively undifferentiated type.

Irradiation was administered by means of a 5 Gm. radium pack at 6 cm. distance, 25,000 mg. to each of three areas with portals of 8 by 10 cm. A biopsy on June 23 was reported as showing "no tumor cells."

The patient is now being treated by plastic surgeons in an effort to cover the ulcerated area after an exceptionally good result was obtained after irradiation.

DISCUSSION

DR. S. IRGANG: There is no actual proof that this patient had granuloma inguinale. I doubt whether cases have been reported of development of malignant changes in lesions of granuloma inguinale. In this case, however, the lesion at the outset may have been granuloma inguinale, since it first appeared eight to nine years ago.

DR. ORLANDO CANIZARES: I think carcinoma in granuloma inguinale is far from uncommon. One of the first patients treated with streptomycin at Bellevue had carcinoma, and we wondered why the condition did not respond. Biopsy revealed the reason.

DR. NATHAN SOBEL: I have had the same experience as Dr. Canizares. Several years ago I had a patient who was definitely proved to have granuloma inguinale covering the entire glans penis. The condition improved, and the patient was lost from observation for about a year. He came back with a lesion which was clinically typical granuloma inguinale; we could not find any Donovan bodies this time in the scrapings from the lesion, and biopsy showed epithelioma. We have had another case, of a lesion on the cervix in which we found Donovan bodies; the patient later acquired epithelioma of the cervix. Greenblatt stated "occasionally, superimposed malignancy has been found to complicate the picture." (Greenblatt, R. B.: Management of Chancroid, Granuloma Inguinale and Lymphogranuloma Venereum in General Practice, Ven. Dis. Inform., 1943, supp. 19. In Greenblatt's bibliography there was a reference to Cardwell, E. S. and Pund, E. R.: Malignancies Related to Venereal Disease; Development of Carcinoma Secondary to Venereal Lymphogranuloma and Granuloma, and Carcinoma. *J. M. A. Georgia* **29**:60-62, 1940.)

DR. CHARLES S. MILLER: Drs. Eliassow and Philips observed this patient for about five months at Queens General Hospital. Donovan bodies were found, and the patient responded very well to treatment.

DR. MAURICE J. COSTELLO: I believe that squamous cell epithelioma is observed most frequently in combination with granuloma inguinale, of all the venereal diseases, at the site of the disease.

DR. FRANK C. COMBES: I am glad to get that evidence from Dr. Miller. We assumed that the patient had granuloma inguinale. I think epitheliomatous degeneration is rather rare, but it certainly does occur. We have seen many such cases.

Xanthoma Diabeticorum. Presented by DR. CHARLES S. MILLER.

DISCUSSION

DR. HOWARD T. BEHRMAN: The case is rather typical. I feel that the term is a bad one, however. Xanthoma diabeticorum points toward one specific factor, and this factor is not the mechanism underlying this cutaneous disease. The eruption occurs in diabetes, but we also see hyperlipemia, which is the responsible factor. Any other xanthomatosis or biliary cirrhosis will produce a similar lesion. I think we should use the term xanthoma eruptivum.

DR. WILBERT SACHS: If you are going to object to the term diabeticorum you had better complain about xanthoma, too. There are few diseases where the

term should be included, for there are only one or two real types of xanthoma. Even though the diabetes itself is not responsible for the development of this type of disturbance, it is certainly indirectly responsible in one way or another. So I believe the usual term is a good descriptive one.

Extensive Tuberculosis Colliquativa. Presented by DR. TIMOTHY J. RIORDAN.
Subungual Verrucae. Presented by DR. TIMOTHY J. RIORDAN.

MINNESOTA DERMATOLOGIC SOCIETY

Robert R. Kierland, M.D., *President*
E. T. Ceder, M.D., *Secretary*
Nov. 4, 1949

A Case for Diagnosis: Lupus Vulgaris? Presented by DR. G. C. DOYLE, Duluth, and DR. J. F. SCHMID, Duluth.

R. W., a 28 year old male filling station operator, noted an eruption on the lip in May 1949. Initially the lesion was erythematous, and the patient thought he had a "cold sore." When he was first examined, on Aug. 16, 1949, he showed a 2 cm. erythematous and vesicular plaque on the left upper lip and an excoriated papular eruption on the flexors of the forearms. There was no history of traumatic injection of oil or grease into the lip.

The reaction to old tuberculin intradermal testing (0.1 mg.) was 4 plus, and the roentgenogram of the chest revealed no abnormality on Sept. 23, 1949. Sputum examinations have not demonstrated tubercle bacilli. Precipitation tests for syphilis gave negative reactions. Calciferol (drisdol®), 100,000 units per day, has been administered since Sept. 27, 1949. On October 4 the dose was increased to 150,000 units per day. There has been some flattening of the lesion and no change of the weight and hemogram. Anorexia or drowsiness has not been experienced.

Cutaneous biopsy, done on Sept. 6, 1949, disclosed in the midcutis granulomas composed of a peripheral zone of mononuclear cells, epithelioid cells and Langhans' type of giant cells. Large areas of central necrosis were present in one section. Ziehl-Neelsen staining failed to demonstrate tubercle bacilli.

DISCUSSION

DR. HARRY FOERSTER, Milwaukee (by invitation): I haven't seen a case of this type of tuberculosis for some time and was first inclined to regard it as miliary sarcoid. The histologic picture, however, supports a diagnosis of lupus vulgaris disseminatus.

DR. CARL W. LAYMON, Minneapolis: To me the most likely diagnosis in this case was lupus miliaris. The lesions were grouped around the eyes, at the sides of the nose and in the perioral region. In one of the sections there was considerable caseous necrosis which would also be compatible with a diagnosis of lupus miliaris.

DR. GUSTAV RIEHL, Vienna, Austria (by invitation): When I examined this patient I did not think he had lupus vulgaris. I called the condition either sarcoid or disseminated miliary lupus. The microscopic picture is not conclusive. In miliary lupus one had best use the older methods of treatment, for vitamin D therapy has not been satisfactory.

DR. H. E. MICHELSON, Minneapolis: I am under the impression that this is a case of lupus vulgaris. The lesions are asymmetric. They are definitely those of lupus nodules. There is no central change in the papules, and the pathologic picture fits very well with that of lupus vulgaris. It is odd that the patient has not shown a response to vitamin D, but there is a possibility that this condition is a type that does not respond to that remedy well.

DR. STEPHEN ROTHMAN, Chicago: The clinical appearance of this lesion is definitely not that of lupus vulgaris. Under glass pressure lupus vulgaris lesions show single, well circumscribed brownish yellow spots in an area that previous to the pressure displayed diffuse red-brown discoloration. The patient does not show this phenomenon. There appears a diffuse brown color on glass pressure. Lack of response to vitamin D_2 also militates against the diagnosis of lupus vulgaris. Lupus miliaris disseminatus may be considered, but the high tuberculin sensitivity of the patient speaks against that diagnosis; remarkably, in lupus miliaris disseminatus, the only skin tuberculosis in which regular tubercle formation with central caseation is seen, most patients are anergic.

A Case for Diagnosis: Granuloma (Type ?)? Incontinentia Pigmenti? Presented by DR. ORVILLE E. OCKULY, St. Paul.

Baby S. J., a 5 month old child, presented at birth an elevated, sharply defined, plateau-like red infiltrated plaque on the left ankle, 2 by 5 cm. in diameter.

DISCUSSION

DR. FRANCIS W. LYNCH, St. Paul: When I first examined this patient with Dr. Ockuly, I considered ectodermal defect and various nevoid conditions. Later, there was slight resemblance to the plaque form of urticaria pigmentosa. No diagnosis yet suggested seems satisfactory.

DR. ROBERT R. KIERLAND, Rochester: I thought, as Dr. Lynch suggested, of urticaria pigmentosa. Some of you will remember a case presented at the meeting in Rochester in which the lesions were similar and were multiple rather than solitary as presented by this young patient. We missed the diagnosis for a long time because we used polychrome methylene blue, which showed nothing; however, the Giemsa stain did reveal characteristic features. The nodular type of urticaria pigmentosa seems to have quite a different course than the macular type usually seen.

DR. STEPHEN EPSTEIN, Marshfield, Wis.: I thought this was a very peculiar case. I have no diagnosis to offer, but I have thought that this case might possibly belong to those ectodermal defects which have been described as incontinentia pigmenti. We know that the pigmentary change represents a late phase of the disorder. It begins as a congenital inflammation which can be demonstrated at least microscopically. There is one clinical type which originates with severe localized infiltration of the skin and a tendency to produce blisters; sometimes microscopically visible blisters and somtimes only crusted lesions are noted. We had a case of this type for which we missed the diagnosis. The clinical course of the case presented here would fit in somewhat with a localized incontinentia pigmenti; however, all the cases reported in the literature had multiple lesions.

DR. CARL W. LAYMON, Minneapolis: I remember Dr. Epstein's case of incontinentia pigmenti in which there were vesicles in addition to the pigmentary changes. I don't believe that there has ever been a case of localized incontinentia pigmenti reported.

DR. ORVILLE E. OCKULY, St. Paul: When first seen the lesion was slightly smaller than it is at present. The crust covering the lesion was floating over seropurulent exudate. The base of the ulcer has appeared the same on each examination. We were impressed by the indolent character of this base which at no time suggested a traumatic factor and has shown no tendency to heal. For the past four or five days streptomycin ointment has been used. There appears to have been some slight improvement during that time.

A Case for Diagnosis: Pyogenic Granuloma? Presented by DR. FRANCIS W. LYNCH, St. Paul.

Mrs. K. H., aged 29 years, has lesions in the right ear which have been present for about five years. The condition has improved during each pregnancy and is

worse with menstruation. This disorder was first noted immediately after a pregnancy. Treatment by cauterization had been attempted on several occasions without much benefit.

Biopsy was performed on March 25, 1949, with electrocautery applied to one lesion only. The sections have not led to a diagnosis, but it is thought that hemangioendothelioma can be excluded. Nitrofurazone (furacin®) has been applied for a prolonged period with slight improvement.

In the right ear canal and nearby on the auricle there are about eight rounded pale blue to blue-red papules 1/16 to 1/8 inch (0.16 to 0.32 cm.) in diameter.

DISCUSSION

DR. FRED T. BECKER, Duluth: I should suggest a diagnosis of congenital auricular fistula. In examining the lesion, I saw a small delled opening which, on pressure, exuded a small amount of serosanguineous material. I think that if this area were injected with methylene blue the fistulous tract could be found in the area of the ear.

DR. ROBERT R. KIERLAND, Rochester: Dr. Becker's suggestion would not explain the papules and minute nodules within the ear. A patient was presented last year, discussed by Dr. Laymon, in whom the diagnosis of pericytoma was seriously considered. The picture presented by this patient is similar. In addition, the story of exacerbation of the lesion at the time of the menstrual period would indicate that endometriosis should be considered.

DR. CARL W. LAYMON, Minneapolis: Was there a histologic section from this case? The condition could be a granuloma telangiectaticum. Pericytoma, a tumor closely related to hemangioendothelioma, should at least be considered in the diagnosis.

DR. FRANCIS W. LYNCH, St. Paul: A most interesting feature is the association of changes with ovulation and pregnancy. I believe hemangioendothelioma can be excluded; we are probably dealing with a peculiar angioma or granuloma.

DR. STEPHEN ROTHMAN, Chicago: In the section presented a hemangiomatous picture prevails. The change during pregnancy is probably due to changes in the hemodynamics of the whole body. "Red palms" also may become manifest or exaggerated during pregnancy.

DR. H. E. MICHELSON, Minneapolis: The general pathologist has a much broader view of the term pyogenic granuloma than we have. He calls almost any form of circumscribed granulation tissues pyogenic granuloma. I think we apply both a clinical and a pathological interpretation to the term.

DR. CARL W. LAYMON, Minneapolis: I have always believed that the terms pyogenic granuloma and granuloma telangiectaticum were synonymous. Weidman, however, made a distinction: In the former pyogenic elements predominate in the histologic picture, while in the latter there is a great proliferation of new blood vessels.

Multiple Perianal and Sebaceous Cysts. Presented by DR. JOHN F. MADDEN, St. Paul.

Mrs. J. S., a white woman aged 36, noticed small nodules around the anus about 12 years ago. These nodules were painless and did not cause her any discomfort until 1948, when they seemed to increase in size and become painful. The anus is ringed with glass-pinhead-sized to pea-sized papules which contain a white sebaceous substance. The lesions are freely movable and do not show any gross evidence of inflammation.

DISCUSSION

DR. L. A. BRUNSTING, Rochester: I think these are exaggerated perianal comedones, perhaps in the form of obstructed apocrine glands which constitute a form of hidradenitis suppurativa when they become infected.

DR. JOHN F. MADDEN, St. Paul: The proctologist says that there are not ordinarily any sebaceous glands or hair follicles in the anal mucosa and that when they are present they generally become enlarged and require surgical excision.

DR. STEPHEN ROTHMAN, Chicago: Embryologically, the apocrine glands derive from the follicular epithelium. Whenever apocrine glands are found, hair follicles are present, too.

Leukokeratosis Oris. Presented by DR. FRANCIS W. LYNCH, St. Paul.

DISCUSSION

DR. STEPHEN ROTHMAN, Chicago (by invitation): I should like to ask how this condition is interpreted. Is it a developmental anomaly, or is it leukoplakia?

DR. FRANCIS W. LYNCH, St. Paul: Some of the older authors on congenital anomalies have used the term leukokeratosis oris, but white sponge nevus has been applied more recently. The condition can be differentiated from leukoplakia or lichen planus and moniliasis. Treatment of this condition has been suggested, but I believe the eruption can safely be left untreated in this patient.

A Case for Diagnosis: Pseudopelade? Presented by DR. CHARLES D. FREEMAN JR., St. Paul.

Pseudopelade. Presented by DR. JOHN F. MADDEN, St. Paul.

DISCUSSION OF THE PRECEDING TWO CASES

DR. CARL W. LAYMON, Minneapolis: There wasn't much atrophy or scarring in either case. It was my opinion that the female patient has pseudopelade, but I was uncertain as to the diagnosis in the boy. As Dr. Lynch pointed out, the lesions in alopecia areata may occasionally appear depressed. Pseudopelade is extremely rare in children.

DR. JOHN F. MADDEN, St. Paul: There have been cases of pseudopelade reported in small children. Ormsby, among others, so stated.

DR. CARL W. LAYMON, Minneapolis: About 1910 there were two or three epidemics of patchy baldness which occurred in asylums and homes for boys around Boston. The disease was called alopecia parvimaculata. These cases occurred in children. The exact nosologic position of this disorder is still uncertain.

A Case for Diagnosis: Periarteritis Nodosa? Thrombophlebitis Migrans? Presented by DR. FRANCIS W. LYNCH, St. Paul.

DISCUSSION

DR. L. A. BRUNSTING, Rochester: Periarteritis nodosa is a variable disease. Recently I observed a man who received treatment with ACTH for periarteritis nodosa; for a time there was pronounced improvement, but later death occurred from cardiac complications. On postmortem examination there was no evidence of active lesions, only decided fibrosis where the vessels had been involved.

A Case for Diagnosis: Dermatomyositis? Generalized Anasarca? Presented by DR. JOHN F. MADDEN, St. Paul.

Diabetes Mellitus Mal Perforans. Presented by DR. JOHN F. MADDEN, St. Paul.

Lichen Planus. Presented by DR. JOHN F. MADDEN, St. Paul.

A Case for Diagnosis: Lupus Vulgaris? Presented by DR. G. C. DOYLE, Duluth, and DR. J. F. SCHMID, Duluth.

Argyria. Presented by DR. FRANCIS W. LYNCH, St. Paul.

Hemosiderosis (Schamberg's Disease? Stasis Dermatitis?). Presented by DR. JOHN F. MADDEN, St. Paul.

Hemosiderosis (Schamberg's Disease? Purpuric Lichenoid Dermatitis?). Presented by DR. JOHN F. MADDEN, St. Paul.

Arsenical Keratoses? Squamous Cell Epithelioma. Presented by DR. JOHN F. MADDEN, St. Paul.

Multiple Superficial Basal Cell Epitheliomas. Presented by DR. JOHN F. MADDEN, St. Paul.

A Case for Diagnosis: Ulcer of the Scalp; Pyoderma? Presented by DR. ORVILLE E. OCKULY, St. Paul.

A Case for Diagnosis: Recurring Generalized Exfoliative Dermatitis; Atopic Eczema? Presented by Dr. John F. Madden, St. Paul.

Multiple Epitheliomas; Generalized Eruption (Atopic Dermatitis?). Presented by Dr. Francis W. Lynch, St. Paul.

Hodgkin's Disease with Possible Hodgkin's Disease of the Skin. Presented by Dr. John F. Madden, St. Paul.

A Case for Diagnosis: Telangiectasia Macularis Eruptiva Perstans? Presented by Dr. John F. Madden, St. Paul.

Lymphangioma of the Tongue. Presented by Dr. Francis W. Lynch, St. Paul.

Transitory Benign Plaques of the Tongue in an Infant. Presented by Dr. John F. Madden, St. Paul.

Lupus Erythematosus of the Face. Presented by Dr. Charles D. Freeman Jr., St. Paul.

Lichen Planus of the Legs. Presented by Dr. Charles D. Freeman Jr., St. Paul.

Syphilis? Lupus Erythematosus? Presented by Dr. Charles D. Freeman Jr., St. Paul.

Congenital Ectodermal Defect. Presented by Dr. Charles D. Freeman Jr., St. Paul.

A Case for Diagnosis: Dermatitis Herpetiformis? Presented by Dr. Francis W. Lynch, St. Paul.

CHICAGO DERMATOLOGICAL SOCIETY

Carl W. Laymon, M.D., *President*

James R. Webster, M.D., *Secretary*

Nov. 16, 1949

Leiomyoma Cutis. Presented by Dr. F. E. Senear and Staff.

R. O., a 37 year old white woman, was seen with three small nodules on the right forearm of 21 years' duration. The lesions had been increasing in size gradually and in the previous six months had developed a "pinching feeling." Pain was experienced on exposure to cold. There had been no previous treatment.

The three grouped pea-sized nodules on the extensor surface of the right forearm were firm and brownish red. They were moderately tender to touch.

Examination of a section taken from one nodule on the right forearm revealed interlacing bundles of smooth muscle traversing the corium in various directions. The muscle fibers contained centrally located, thin, very long, blunt-edged nuclei. The muscle bundles were easily distinguishable from the collagenous tissue. A Van Gieson–stained section, also submitted for study, revealed the muscle fibers as yellow bundles in contrast to the dark orange–stained collagenous tissue.

DISCUSSION

Dr. Oliver S. Ormsby: This is one of the rare diseases of the skin. The lesions are dull red, yellowish or violaceous translucent or brown nodules. One might practice twenty-five years seeing a large number of patients and never see one of these cases. The condition is a tumor of the muscle of the skin. Sometimes that tumor arises from the arrectores pilorum and sometimes from the muscle of the blood vessels themselves. It is very painful when the patient is exposed to cold. The pain is continuous for some time until the lesion gets warmed up again. The condition is very resistant to treatment. Roentgen rays have no effect, and solid carbon dioxide has no effect other than to relieve the pain. There is only one method of removing the lesion, and that is surgical, and even after surgical treatment the lesion sometimes recurs.

The cases I have studied have been more extensive than the one you saw here today, though this is a very characteristic lesion. It is very hard, and no application of any sort has the slightest effect on it. We do not know what makes this muscle tumor grow, but we do know that it is a muscle tumor arising from one of the sources I have already mentioned. I have taken care of these cases for a number of years, and all that time there has been no change in the lesions. The condition is always painful and sensitive to pressure and seasonal changes. Altogether it is a very interesting disease of the skin.

Dr. Theodore Cornbleet: It is interesting not only that this patient has pain when exposed to cold, but, furthermore, that the greatest discomfort is

felt when she has "gooseflesh," which observation would point to the arrectores pilorum as the source of these tumors.

DR. ADOLPH ROSTENBERG JR: As Dr. Ormsby pointed out, there are several possible muscle sources for these tumors. There are two chief muscle sources, either the muscles of the pilomotor apparatus or those of the sweat glands. It is possible to distinguish between these on pharmacological grounds. There was an interesting study published in *Clinical Science* (**7**:29 [July] 1948) in which a woman who had leiomyoma cutis was treated with cholinergic drugs. It was found that these would cause a contraction of the tumor muscle. There was no response to adrenergic drugs. It was concluded that the tumor was derived from muscle of sweat gland origin.

DR. EARLE PACE: At Dr. Caro's suggestion I attempted solid carbon dioxide therapy in a case of this sort. The patient had some 15 or 20 nodules on the arm and a few scattered elsewhere on the body and leg. All were rendered free of pain after the treatment with solid carbon dioxide in two or three attempts. Excision would have been impractical on account of the number of lesions.

Lipomelanotic Reticular Hyperplasia of the Lymph Nodes; Scaly Eruption on Trunk. Presented by DR. CLEVELAND J. WHITE.

Mrs. A. C., a housewife aged 38, states that in August some "sores" appeared in the mouth while she was under gold treatment for rheumatoid arthritis. Though the medication was discontinued and the oral lesions disappeared, there developed a generalized patchy eruption on the trunk, which has continued intermittently until at the present time there is a symmetrical erythematous scaling eruption on the trunk and on the extremities.

Two months ago the patient noticed an enlargement in the right groin and later in the left groin. These enlargements have persisted. The glands are rather discrete and not very tender but very much enlarged, especially on the right side. There has been occasional adenopathy elsewhere.

A soothing local medication has been used as well as roentgen therapy in fractional doses and symptomatic treatment.

The laboratory examinations have revealed nothing abnormal. Blood sugar has been normal. The last leukocyte count was 8,700, with 25 per cent lymphocytes, 73 per cent polymorphonuclear cells and 2 per cent eosinophils.

A lymph node was removed, and the section here presented showed a deposit of melanin and sudanotropic droplets with a pronounced reticular hyperplasia with slight distortion of the normal architecture of the node.

Biopsy of the skin showed ordinary mild inflammation.

The case is presented because attention was recently called to this syndrome by Laipply. He presented six cases, two of which developed into lymphoblastoma. He expressed the opinion, however, that the adenopathy is probably benign.

DISCUSSION

DR. S. M. BLUEFARB: This case presents all the clinical features of lipomelanotic reticular hyperplasia, namely, erythroderma, pigmentation and enlargement of the superficial lymph nodes. Histologically, there is an increase in number and in size of all the lymph follicles. Although the majority of these changes are benign and reversible, one should not overlook the fact that occasionally transformation into one of the lymphoblastomas may occur. Dr. Webster and I have made a report of two cases, to be published in the near future in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY (**61**:830 [May] 1950), in which the disease started as lipomelanotic reticulosis and eventuated into mycosis fungoides.

DR. STEPHEN ROTHMAN: A male patient with the same diagnosis and with severe neurodermatitis was shown here several months ago. Could somebody tell us something about the further course in that case?

DR. MILTON ROBIN (by invitation): That patient has been followed by those in the psychosomatic clinic of the Michael Reese Hospital. From the clinical, pathological and hematological standpoint, including sternal marrow study, there has been no evidence of lymphoblastoma.

Under dermatological and psychologic therapy the skin disease has improved decidedly. At times there has been complete clearing of the generalized eruption. The exacerbations have been mild and do not require periods of hospitalization as in the past.

Small Plaques on Scalp in a 42 Year Old Woman (Lymphoblastoma?). Presented by DR. JAMES R. WEBSTER and (by invitation) DR. OLIVER RIAN.

Mycosis Fungoides with Poikiloderma-like Changes in a 67 Year Old Man. Presented by DR. E. A. OLIVER and Staff.

Lymphoblastoma of Undetermined Type. Presented by DR. FRANCIS E. SENEAR and DR. IRENE NEUHAUSER.

A. V., a white man aged 59, was first seen in 1946 with a dollar-sized infiltrated patch covered with psoriasiform scales on the right shoulder which had been present eight to ten years. He also had a few superficial scaling patches with slightly raised margins on the left thigh. The lesions on the thigh were of recent development and disappeared with topical therapy, but the patch on the shoulder has persisted to the present time.

The patient was seen again in January 1949, presenting a number of lesions on the trunk and extremities which were of two distinct types. He had a few lesions on the lower extremities which were dark red and indurated and had the clinical appearance of superficial erythematoid epithelioma. The remaining lesions were erythematosquamous plaques, clinically resembling parapsoriasis en plaque. One of the lesions on the leg was examined histologically, and a diagnosis of lymphoblastoma of undetermined type was made. Examination of the blood and bone marrow showed no abnormal conditions.

The patient was recently hospitalized for persistent occipital headaches. He now presents a third type of lesion. In addition to the two types of lesions already described he has several fairly well marginated superficial ichthyotic-looking patches on the left thigh and leg. The blood picture has remained normal. There are no subjective symptoms.

DISCUSSION OF PRECEDING THREE CASES

DR. STURE JOHNSON, Madison, Wis.: Recently a case similar to that of Drs. Webster and Rian was reported by Drs. Pohle and Juhl from the roentgen ray department of the University of Wisconsin (Leukemia Cutis of Scalp, *Wisconsin M. J.* **48**:223, 1949). The results of peripheral blood and sternal marrow studies were repeatedly negative in spite of the skin section which showed an infiltrate suggestive of a lymphocytic leukemia or a lymphosarcoma. Roentgen ray therapy caused the nodules to disappear rapidly.

DR. STEPHEN ROTHMAN: In the first case the clinical appearance of the lesion, the softness of the infiltrate and the purple color with a few telangiectases are rather characteristic for lymphatic leukemia.

DR. M. H. EBERT: It is well to recall that there are several ways in which mycosis fungoides may develop. In the majority of cases it is by generalized itching with nondescript lesions which are later followed by the mycotic stage. The d'emblée type with the primary appearance of tumors is less common. Rarely one sees the disorder begin with poikiloderma-like changes in the skin. Dr. Oliver has already had one case of that type, and I believe the present one is another. A fourth type, in which the disease begins with generalized erythroderma, is not universally accepted by all dermatologists.

DR. S. M. BLUEFARB: The first report of poikiloderma changing into mycosis fungoides in the American literature was that by John Lane (ARCH. DERMAT. & SYPH. **4**:563 [Nov.] 1921), who also cited the case presented by Dr. Ormsby before the Chicago Dermatological Society in 1916 (*J. Cutan. Dis.* **35**:42, 1917). Since then numerous instances of the transition of poikiloderma into mycosis fungoides have been reported in the world literature, particularly in French dermatological journals, and Dr. E. A. Oliver completely reviewed this subject in 1936 (ARCH. DERMAT. & SYPH. **33**:267 [Feb.] 1936). The case presented here is another of this group, showing the development of a poikiloderma-like syndrome into mycosis fungoides.

Generalized Myxedema: Basal Metabolic Rate, —19. Presented by DR. E. A. OLIVER and Staff.

Localized Myxedema and Exophthalmos; No History of Thyrotoxicosis. Presented by DR. E. A. OLIVER and Staff.

DISCUSSION OF PRECEDING TWO CASES

DR. M. J. REUTER, Milwaukee: It was my impression that in the second case I could palpate discrete nodules on the legs, which point brings up the question of some type of vascular disease of the extremities. A point I think against generalized myxedema in the first case is that the patient had a basal metabolic rate of — 19. In these cases of myxedema in which there are definite cutaneous observations there is a basal metabolic rate of — 40 or more. A biopsy taken a little deeper, so as to include the subcutaneous fat and larger vessels, might be of help. The biopsy that was shown exhibited much more inflammatory changes than one would expect in ordinary myxedema.

DR. STEPHEN ROTHMAN: I feel the same way as Dr. Reuter does. I never saw myxedematous skin with a basal metabolic rate of — 19, and I was not impressed with the changes as being characteristic of myxedema.

Concerning the case of localized myxedema, I fully agree with the diagnosis. The case history is rather typical. In this connection I should like to correct a misprint in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY (**58**:526, 1948). I said that this condition is always associated with hyperthyroidism—not with hypothyroidism, as the statement was printed. Therapeutic results with local injections of hyaluronidase have not been impressive so far in this condition.

DR. S. J. ZAKON: The reason for the basal metabolic rate of — 19, which caused some to doubt the diagnosis of generalized myxedema, may be that the patient was on treatment with thyroid extract for a number of years.

Localized myxedema and exophthalmos in a patient who had no previous medication or surgery for thyrotoxicosis is rather rare. This condition is a paradoxical one, and many theories have been propounded to explain this phenomenon. The recent excellent paper of Curtis and his associates not only reviewed the entire subject of progressive exophthalmos and localized myxedema but also introduced a new hypothesis as to the role of the pituitary gland in the production of both progressive exophthalmos and localized myxedema.

The concept of a thyroid-pituitary axis may explain the therapeutic failures with thyroid. Perhaps the use of filtered roentgen ray therapy to the pituitary gland, as recently suggested by W. O. Thompson, and the use of hyaluronidase enzyme may throw some more light on this subject.

Dermatitis Factitia. Presented by DR. M. H. EBERT and (by invitation) DR. B. YAFFE.

A. C., a white woman aged 34, first acquired scarring lesions about the chin and face in 1943. Since that time she has consulted many physicians and has received many kinds of remedies. At present the shoulder girdle, arms and legs are also involved.

DISCUSSION

DR. THEODORE CORNBLEET: This young woman has had from 20 to 25 different jobs and does not know why she is unable to remain at any one of them. She thinks that perhaps people do not like her. I believe this observation points to the probability that the patient has a personality disorder. It may even derive from a real psychosis. I think the opinion and advice of a psychiatrist are needed.

DR. L. F. WEBER: I should like to suggest the name neurotic excoriations. I think patients who have dermatitis factitia are those who try to deceive us. This patient is not trying to deceive. She admits she produces these lesions.

DR. THEODORE CORNBLEET: As Samuel Butler said long ago,

He that complies against his will
Is of his own opinion still.

The young woman admits she herself produces the lesions. I think that what is more important ultimately to the patient is not whether we call this disorder dermatitis factitia or neurotic excoriations but rather why she mutilates herself. There is some personality disorder, though its nature and what to do about it is more a matter for psychiatrists than for us.

DR. STEPHEN ROTHMAN: I cannot agree that neurotic excoriations and hysterical self mutilation with extensive and deep scarring such as we see in this case are the same thing. Most patients with neurotic excoriations readily admit that they dig their skin with their nails; in the majority of cases it is easy to educate them not to do so. The underlying neurosis is usually not severe; in many cases the digging is just a bad habit. Self mutilation by chemicals is a most severe manifestation of conversion hysteria; the patients will not admit that their lesions are self inflicted unless the corpus delicti, the small bottle with the acid or other caustic chemical, is found and shown to the patient. Of course, these patients should be sent to the psychiatrist, and I believe we all do send them there. However, I am sorry to say that I have had very little help, if any, from modern psychiatry in such cases. I wonder how others feel about this.

DR. M. H. EBERT: A most important point in favor of a diagnosis of dermatitis factitia is the fact that the patient takes great enjoyment in the fact that she has confounded so many physicians. She dwells on the fact that no one has been able to diagnose what she believes to be a very obscure disorder. Whether we call her condition dermatitis factitia or label it neurotic excoriations is a matter of definition. Occasionally there is a case like this where we must straddle. Clinically the lesions are those of neurotic excoriations, but the peculiar mental element is that of dermatitis factitia.

Lymphangioma of the Dorsum of the Tongue. Presented by DR. THEODORE CORNBLEET.

P. deJ., a white boy 5 years old, has had a lesion on the dorsum of his tongue since the age of 3 years. The mother noted the lesion at its full size, without previous or later growth.

It is for the most part the color of the tongue, with elements of yellowish white and dark red. There is a central irregular flat mamillated plaque with outlying vesicle-like lesions. There is no induration or subjective sensation.

Suggestions as to therapy will be entertained.

DISCUSSION

DR. STEPHEN ROTHMAN: Therapy of this condition was discussed at the last meeting of the Minnesota Dermatologic Society. It was agreed that one should leave lymphangiomas of the tongue alone as long as they do not cause real trouble. If, because of traumatization, pain or hemorrhage, treatment becomes necessary, radiation therapy is quite satisfactory in most cases.

DR. L. F. WEBER: I have treated two patients with solid carbon dioxide with good results, and in one patient, a girl about 18 years old, there was an excellent result from radiation therapy.

Nevus Comedonicus of Axilla. Presented by DR. F. E. SENEAR and Staff.

DISCUSSION

DR. EARLE PACE: I should like to ask whether anyone has had any luck with therapy other than surgery in nevus comedonicus. I have the impression that a recently treated case occurring in a more typical area (the right side of the neck) responded rather well to large doses of vitamin A and the local use of a salicylic acid cream.

Lichen Planus, Conjunctival Involvement. Presented by DR. STEPHEN ROTHMAN.

Lichen Planus in a Patient Who Had Lichen Nitidus One Year Previously. Presented by DR. THEODORE CORNBLEET and (by invitation) DR. H. SCHORR and DR. S. BARSKY.

DISCUSSION OF CASES OF LICHEN PLANUS

DR. STURE JOHNSON, Madison, Wis.: Conjunctival involvement by lichen planus is in my experience rare though various observers have said that this manifestation is often present. Photophobia as well as corneal injection was present in the first case. These two manifestations I believe are toxic in origin and probably due to some medication used for the lichen planus rather than the lichen planus itself.

DR. JULIUS E. GINSBERG: In the first case I think the lesions in the mouth look a good deal like a type of leukoplakia we see in lichen planus, but it occurred to me that the condition might be lupus erythematosus. The patient has a lesion of the external auditory canal and pinna which is scaling and atrophic and resembles very much lupus erythematosus. There are no characteristic lesions of lichen planus on the body at the present time according to my examination.

DR. M. R. CARO: In connection with the second case, I like whenever possible to interpret all the lesions on a patient on the basis of one diagnosis. In this case that is impossible. The sections taken from the previous lesion could not be accepted for lichen planus. I am fairly certain that the diagnosis was originally lichen nitidus. At the present time, however, the lesions clinically and histologically are characteristic of lichen planus.

DR. STEPHEN ROTHMAN: The first patient had clinically and histologically typical lichen planus of her skin and still has the disease on the mucous membranes of the mouth. The conjunctivitis has been described by the ophthalmologists as showing extremely severe inflammation with a necrotizing tendency. However, the cornea and iris are not involved. From the literature three cases of conjunctival involvement in lichen planus could be collected.

A Case for Diagnosis: Dermatitis Factitia? Epidermolysis Bullosa (Acquired? Congenital Tardive?)? Presented by DR. JULIUS E. GINSBERG and (by invitation) DR. J. E. SCHREIDER.

F. G., a 43 year old white man, complained of abnormal separation of "layers of skin," so that ordinary trauma caused damage, the resulting lesions healing very slowly. When first examined two months ago, the patient had about ten 3 to 8 mm. vesicles, superficial ulcerations and abrasions on the dorsa of the fingers and hands. He stated that such lesions had been appearing almost continuously since the onset three and one half years ago. Blood count and results of urinalysis were found to be within normal limits. After the third visit, the

character of the lesions altered; they became more regular and punched out and had deep red nonpurulent bases. There were, in addition, some vesicles with almost no inflammatory base. The patient has since presented frank vesicles and bullae, always without the inflammatory base. He states that he does not handle any unusual chemicals. He also states that the lesions arise spontaneously on red spots; then a blister forms and breaks, and the lesion heals very slowly. There is no familial history of such lesions as the patient has. He states that mosquito bites leave no welts. There is no history of chronic alcoholism. The urine does not darken on standing in light for two days.

DISCUSSION

DR. STURE JOHNSON, Madison, Wis.: This patient's family history is negative for epidermolysis bullosa, and the tendency to develop bullae following trauma has been present on the hands for only four years. The patient has lost 20 pounds (9 Kg.), probably because of a diet, and has had clubbed fingers as long as he can remember. The etiological factors for these two observations should be evaluated further. The patient has never had neuritis, gastrointestinal colic or dark-colored urine or demonstrated sensitivity to sunlight. In spite of this, I believe porphyria or some toxic process should be suspected. In the patient with uncontrolled diabetes I have seen bullous lesions, particularly on the extremities. Whether diabetes, as well as other metabolic disturbances, accounts for cases of so-called acquired epidermolysis bullosa is difficult to say and needs further investigation.

DR. F. R. SCHMIDT: This patient presented a type of eruption that Brunsting and Mason (Porphyria with Cutaneous Manifestations, *Proc. Staff Meet., Mayo Clin.* **22**:489-494 [Oct. 29] 1947) and Bordo (Bordo, J. M. C.: The Porphyrins and Porphyrias, Buenos Aires, Lopez and Etchegoyen, 1946) associated with disturbances of porphyrin metabolism. These eruptions make their appearance in adults and may be precipitated by excesses in drinking, infection, exposure to sunlight and disease of the liver. In some persons with this syndrome are found amebic dysentery and hepatic insufficiency. A toxic element of some kind usually brings on an attack.

A Case for Diagnosis: Acrodynia? Dermatomyositis? Presented by DR. RUBEN NOMLAND, DR. ROBERT L. BARTON and DR. ROBERT G. CARNEY, Iowa City.

DISCUSSION

DR. STURE JOHNSON, Madison, Wis.: It is my feeling that acrodynia as well as dermatomyositis must be considered in this case. When I obtained a history from the mother that two bottles of a teething lotion had been used, I felt that acrodynia was the diagnosis since some teething lotions contain mercurials, which in the opinion of some constitute one of the causes of acrodynia. In this case I believe pinkness, peeling, paresthesia, perspiration and photophobia are or have been present. The annular erythematous lesions resembling granuloma annulare on the elbows and hands could be one of the many skin manifestations of acrodynia.

DR. STEPHEN ROTHMAN: I agree with the diagnosis of acrodynia in the child. Dr. Johnson's inquiry revealed that this baby was given a teething lotion which contains mercury. The mother has typical lupus erythematosus.

DR. EARLE PACE: I could not get a good look at this child. There were a lot of things that made me think of dermatomyositis. I hope that diagnosis is being considered.

Sensitivity to Cold. Presented by DR. H. H. RODIN.

D. W., a 4½ year old white girl, was first seen Oct. 18, 1949, with a nonpruritic eruption involving the cheeks, neck and exposed portions of the upper and lower

extremities. The mother stated that the eruption was first noticed shortly after birth. Later it was observed that the lesions occurred only on exposure to cold and that the usual length of exposure required to produce an attack was approximately ½ hour. The eruption can be terminated in about one hour by placing the child between several blankets. Except for profuse perspiration no other constitutional symptoms are noted.

The eruption when present consists of numerous edematous papules and urticarial lesions involving the exposed portions of the body. Further examination reveals a well nourished child with normal observations on physical examination.

The history revealed that this child was a full term normal infant except for a mild eruption consisting of scattered "red spots." The medical and surgical history is negative, even to the absence of the usual childhood diseases.

The family history indicates this dermatosis to be present as a dominant, non-sex-linked Mendelian trait (see accompanying figure).

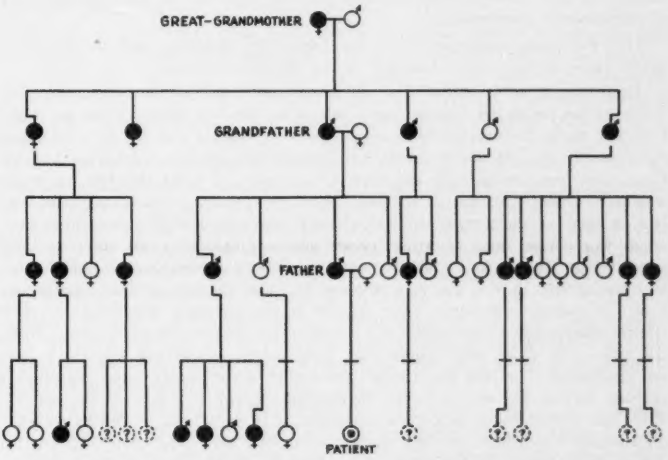

Chart showing family history of sensitivity to cold. Black symbols indicate person showing the trait.

The father, who has a similar condition, states that constitutional symptoms, consisting of profuse perspiration, headache, nausea, abdominal cramps and joint pains, associated with the termination of an attack, did not occur until he reached his late teens (16 to 17 years old).

The onset of these symptoms at approximately the same age is characteristic for other members of the family affected by this disease.

Results of laboratory examination of the blood were as follows:

Date	Red Blood Cells	White Blood Cells	Hemoglobin, %	Polymorphonuclear Cells, %	Lymphocytes, %	Eosinophils, %	Monocytes, %
1/ 5/49	3,930	9,800	74.6	52	38	4	6
4/13/49	4,120	23,800	68	70	21	1	8
7/ 8/49	4,800	12,450	76	56	37	3	4

Urinalysis of a specimen taken Nov. 1, 1949, when the eruption was present, had the following results: reactions—alkaline, with those for albumin and sugar

negative, and several pus cells on microscopic examination. On November 2, when the eruption had terminated results of urinalysis were as follows: reactions —acid, with those for albumin and sugar negative, and several pus cells on microscopic examination.

The porphyrin screening test (Wood filter) gave negative reactions.

DISCUSSION

DR. STEPHEN ROTHMAN: The family tree shows quite clearly the mendelian dominant inheritance of this condition. The patient should be tested for paroxysmal hemoglobinuria, which is often associated with cold urticaria.

As Sulzberger pointed out, it is probable that all so-called physical allergies are based on hypersensitivity to normal metabolites formed in everybody's skin in response to the respective physical stimuli—mechanical stimuli, cold, heat and ultraviolet or visible radiation. The patient acquires (or, in this case, inherits) specific antibodies against these metabolites. The antibodies can be demonstrated by passive transfer. All physical allergies respond favorably to the administration of antihistamine preparations.

DR. THEODORE CORNBLEET: I agree with Dr. Rothman that antihistamine agents show to their best advantage in the physical allergies.

DR. ADOLPH ROSTENBERG JR.: I agree with most of the statements Dr. Rothman has made, but I would put a somewhat different interpretation on them. I do not think that on the basis of the present evidence one should label these cases as allergic. It really should not be necessary to give reasons as to why these cases are not allergic, inasmuch as the onus of proof devolves on those who assert they are, but a tradition based on rhetoric rather than fact has labeled many of these manifestations physical allergies, and it is now incumbent on us to examine these assertions somewhat more critically. In order to label a process as allergic it is necessary that one have a definite antigen which may be manufactured in vivo and as a response to which the host produces antibodies. I am, of course, aware that these are not always or easily demonstrable. The clinical manifestation then arises as a result of the antigen-antibody union. Now, the concept of those who believe that these manifestations are allergic is that the appropriate (for the given case) physical stimulus causes some degradation of body protein and that it is this new protein which then acts as the antigen. From the little I know of protein chemistry, it is very hard to believe that the mild stimuli which often produce manifestations in a given case could alter protein sufficiently to make it antigenic. For example, in the case under discussion, the child will get manifestations if she is out in cold winter weather but will also get the same manifestations in the summer if there is a sudden drop in temperature, as during a thunderstorm. It would thus be necessary to postulate that the child manufactures the same antigen at widely different temperature ranges. This theory does not make sense. Another point against this case and similar ones being on an allergic basis is the beautiful family history. You will recall that the patient's father, grandfather and many relatives have not similar manifestations but identical manifestations. Now, in allergic diseases for which any hereditary tendency has been adduced the manifestation itself is not inherited, but rather the tendency to develop a similar manifestation is inherited. In other words, the child of a parent with, say, asthma from timothy does not inherit timothy asthma but rather inherits the predisposition of the development of an atopic disorder. Thus, the inheritance pattern in the present case is much more akin to those seen in genetic or metabolic anomalies.

It is often asserted that the fact that in some of the so-called physical allergies one obtains successful passive transfer proves that these are on an antibody basis. This is just not so, and until it has been shown that the transferring material is a globulin conforming to the nature of antibodies, all one can say is that in some of these cases there is a material which causes the cells of the recipient to react to a physical stimulus.

A point worthy of mentioning in this case is that the mother states that the child had some lesions at birth.

These remarks are not meant to be merely argumentative or captious but are made because I feel that the glib labeling of all these cases as allergic is wrong and impedes progress because such a label makes us assume that we understand the nature of these cases whereas, in reality, I do not believe that we do.

DR. STEPHEN ROTHMAN: I am sorry that I cannot understand Dr. Rostenberg's point when he says he doubts that physical allergies are true allergies. Like a person who suddenly manifests a violent urticarial type of hypersensitivity to fish or crab meat, another person manifests the same type of hypersensitivity to acetylcholine (as in heat and emotional urticaria), and again another person suddenly acquires hypersensitivity to a substance which is formed in everybody's skin if the ultraviolet wavelengths of 2,800 to 3,100 angstrom units are absorbed (as in ultraviolet solar urticaria). Dr. Cornbleet is correct in stating that in most reported cases of long wave solar urticaria passive transfer was unsuccessful. However, Rajka reported one positive result.

DR. S. M. BLUEFARB: This unusual case is also of interest because the girl has anemia and cold agglutinins are one of the causes of hemolytic anemia. Ham and Castle (Relation of Increased Hypotonic Fragility and of Erythrostasis to Mechanism of Hemolysis in Certain Anemias, *Tr. A. Am. Physicians* **55**:127, 1940) pointed out that stasis results in increased spheroidicity of red cells and, ultimately, in hemolysis. Therefore, they designated hemolysis following agglutination a phenomenon of stasis or "sludging." Bergenhem and Fahraeus (cited by Dameshek: Hematology, *New England J. Med.* **234**:829, 1946) demonstrated that normal blood serum contains a lytic substance, which they called "lysolecithin." They showed that it became increased with stasis and concluded that it was responsible for normal blood destruction in the chief organ of stasis, the spleen. I believe this case should be investigated for cold agglutinins as a possible cause for the hemolytic anemia.

DR. H. H. RODIN, South Bend, Ind.: Of course, a great deal more work remains to be done, but this case had to be presented today because of the inability of the patient to come at any other time. Incidentally, this child is being investigated further by a hematologist.

At the present time I am not certain whether this case should be classified under the allergic diseases. There have been two types of cases reported. For example, Horton and his associates at the Mayo Clinic reported (Hypersensitiveness to Cold, *J. A. M. A.* **107**:1263, 1936) 13 cases in which they were able to show autoagglutinins which were treated with histamine with good results. On the other hand Urbach and co-workers (ARCH. DERMAT. & SYPH. **43**:366-374, 1941) reported a case similar to the one presented in which they could demonstrate nothing in the nature of an allergy and postulated that the disease was a nonallergic type produced by a genetic neurovasomotor disturbance.

There are many peculiar observations that still remain to be explained. For example: why must the cold act on the skin for at least a half hour before symptoms develop? Or, what mechanism delays the onset of constitutional symptoms on termination of an attack until approximately the age of 17 years is reached? Perhaps further studies will bring the answers to these questions.

Black Hairy Tongue. Presented by DR. THEODORE CORNBLEET and (by invitation) DR. D. COHEN and DR. D. MUSGRAVE.

DISCUSSION

DR. A. H. SLEPYAN: I recently saw a man who had erythema multiforme for the third time with lesions involving the mucous membranes of the mouth. When the eruption appeared for the second time about 2½ months ago, he was hospitalized and treated with penicillin. While under treatment he manifested a black hairy

tongue. Several weeks after the lesions cleared he once again appeared with a new eruption. I placed him on aureomycin therapy. A 250 mg. capsule was taken four times a day. The powder was suspended in 60 cc. of water and the contents swished around the mouth for five minutes and then swallowed. At the end of two weeks the black hairy tongue disappeared.

DR. MICHAEL H. EBERT: Some time ago I experimented with aureomycin and took 1 Gm. a day to inhibit the secondary infection of a cold. The next day I read of a case in which black hairy tongue followed the administration of penicillin. I looked at my tongue, and I had a patch 1.5 cm. in length which had appeared as the result of the self-administered aureomycin. That disappeared gradually. My friend, Dr. Slepyan, tells me that aureomycin applied locally cures black hairy tongue. There is not as much contradiction in that statement as may appear. In oral administration there is no contact with the papillae but the drug does interfere with the bacteriological condition of the gastrointestinal tract.

DR. M. J. BRUNNER (by invitation): We are getting a successful result in the treatment of one patient with black hairy tongue with aureomycin administered locally. The patient is still under treatment.

DR. THEODORE CORNBLEET: Last Friday this patient showed the greatest involvement of the tongue I have seen in this disorder. Yet so great has been the degree of improvement since then that now there is scarcely anything wrong to be seen. The patient denied knowingly taking or using drugs. The normal growth and exfoliation of the lingual papillae must be governed by certain growth and retarding influences, and some of these latter must derive from the microorganismal flora in the mouth. The presence of penicillin, other antibiotics and chemicals is capable of upsetting the balance of forces to permit increased papillary growth or cohesiveness. I can visualize the opposite set of circumstances, namely, where these influences are abnormally about to give the tongue a smooth surface.

Sarcoidosis. Presented by DR. HERBERT RATTNER, DR. H. H. RODIN, South Bend, Ind., and DR. D. MUSGRAVE.

DISCUSSION

DR. MICHAEL H. EBERT: I think there are some very interesting features in this case. Actually this woman's sarcoidosis is a systemic disease. She not only has skin disease but also has two big tumors of the upper lids which are due to involvement of the lacrimal glands. She has a nodule over the parotid gland. These observations suggest one point. Heaton and Shannon (Heaton, T. G., and Shannon, E. H.: Mikulicz' Disease, *Canad. M. A. J.* **58**:368-370 [April] 1948) wrote an article about two years ago on what is called the Mikulicz syndrome. The ophthalmologists talk not only of the Heerfordt syndrome but also of the Mikulicz syndrome in which the lacrimal glands are involved. I would call the present case a forme fruste of the Mikulicz syndrome. If one examines these sarcoid cases closely he will always run on to something interesting. It will be interesting to follow this woman and see what the outcome of the disease will be. In spite of the fact that at present she shows no lesion in the lungs or bones, these may follow. As you know, that outcome is not uncommon in this disease.

Hemochromatosis. Presented by DR. THEODORE CORNBLEET and (by invitation) DR. D. COHEN and DR. S. BARSKY.

DISCUSSION

DR. LEONARD F. WEBER: I was thinking about this patient in connection with the question of occupational factors. He had considerable pigmentation on the exposed parts of the face, forearms and neck and some pigmentation of the legs. In his work silvering mirrors he has come into contact with silver for 25 years.

He said he did not come into direct contact with the silver solution. The question arises whether inhalation of any of these substances is likely to cause cutaneous changes. It is my impression that it is not.

DR. M. R. CARO: There is one other point worthy of comment. With the hematoxylin and eosin stain the section showed a tremendous amount of pigment within the epidermis and about the sweat glands. The Prussian blue stain showed the pigment to be hemosiderin rather than melanin. There is also a lot of pigment about the blood vessels. I have never seen hemosiderin so distinctly within the epidermis before. The histologic diagnosis is hemochromatosis.

DR. THEODORE CORNBLEET: This patient presents everything for a diagnosis of bronze diabetes, such as enlarged liver and spleen, glycosuria and abundant iron pigment. As long as the possibility of the presence of silver has been raised, it becomes necessary to look for this metal, and we shall do it. The peculiar cast of the skin seen in argyria, however, is in my opinion lacking in this man.

Lepromatous Leprosy Improved After Treatment with Diasone.® Presented by DR. THEODORE CORNBLEET and (by invitation) DR. D. COHEN and DR. D. MUSGRAVE.

DISCUSSION

DR. F. R. SCHMIDT: To me this is the most interesting case shown today because Dr. Cornbleet and his associates have demonstrated that the sulfone drugs have opened a new and hopeful era for patients with Hansen's disease. Furthermore, they have proved that these patients do not have to go to Carville in order to get well. When you remember that Mycobacterium leprae is aerobic like the tubercle bacillus, the beneficial effect of diasone® (disodium formaldehyde sulfoxylate diaminodiphenylsulfone) in Hansen's disease is understandable. Diasone® contains a reducing substance, sodium formaldehyde sulfoxylate, and this lowers the oxygen tension of the tissues. While in South America I noticed that patients with this disease and also with leishmaniasis are apparently benefited by living in localities situated at high elevations above sea level, where the oxygen tension of the blood is similarly reduced. Lowered oxygen tension of the blood may be induced by the administration of ascorbic acid and glutathione along with cobalt to produce polycythemia. This treatment produces a physicochemical condition of the tissues that is inimical to M. leprae. The host is not harmed, but the invading organism loses its vitality and acid fastness.

DR. H. H. RODIN, South Bend, Ind.: I think this is the first person with leprosy with a positive Wassermann reaction that I have seen at Cook County Hospital who came in without having been treated for syphilis.

DR. JULIUS E. GINSBERG: We have a patient at Hines Hospital who has been coming in for the past year, and we have treated him with promizole® (4,2'-diaminophenyl-5'-thiazolylsulfone). He has been given dihydrostreptomycin as well for a month period on two occasions. This patient had a large accumulation of erythematous macules present over his lower extremities, and the condition would ordinarily be classed as the maculoanesthetic type of leprosy. In each of these accumulations we demonstrated very numerous lepra bacilli. The patient has shown most remarkable response to the use of the two therapeutic agents cited.

DR. THEODORE CORNBLEET: I have under treatment with sulfone drugs a Chinese boy whose skin lesions have regressed very rapidly. Only pigment remains in their place. The newer group of remedies for leprosy, such as diasone® and promin® (sodium p,p'diaminodiphenylsulfone-N,N'-didextrose sulfonate), belongs to the sulfones in general, a division of the sulfonamides. The sulfones are said to be less toxic and to induce fewer idiosyncrasies than the parent group.

Lupus Erythematosus with Basal Cell Carcinoma; No History of Roentgen Therapy. Presented by DR. CLEVELAND J. WHITE and (by invitation) DR. LEONARD S. CRASER.

Acne Vulgaris in a 2½ Year Old Child. Presented by DR. F. E. SENEAR and Staff.

Morphea? Lichen Sclerosus et Atrophicus? Presented by DR. A. H. SLEPYAN and DR. W. N. NEW (by invitation).

A Case for Diagnosis: Pityriasis Rubra Pilaris? Lymphoblastoma? Presented by DR. F. E. SENEAR and Staff.

Granuloma Annulare: Multiple Lesions. Presented by DR. ALBERT H. SLEPYAN.

Keratosis Palmaris et Plantaris (Punctate Variety). Presented by DR. EDWARD A. OLIVER and Staff, Hines, Ill.

Hereditary Hemorrhagic Telangiectasia (Rendu-Osler-Weber Syndrome). Presented by DR. EDWARD A. OLIVER and Staff.

A Case for Diagnosis: Sarcoidosis? Presented by DR. THEODORE CORNBLEET and (by invitation) DR. H. SCHORR and DR. D. MUSGRAVE.

Disseminated Neurodermatitis; Bizarre in Distribution and Color. Presented by DR. MICHAEL H. EBERT and (by invitation) DR. V. LEAF and DR. S. BARSKY.

Sickle Cell Anemia with Leg Ulcer in a 26 Year Old Negro. Presented by DR. J. WEBSTER and DR. S. BLUEFARB and (by invitation) DR. S. BARSKY.

Lymphangioma Circumscriptum of the Buttock. Presented by DR. HERBERT RATTNER and (by invitation) DR. H. H. RODIN, South Bend, Ind., and DR. S. BARSKY.

Pemphigus Foliaceus Following Pemphigus Erythematosus? Syphilitic Aortitis? Presented by DR. MICHAEL H. EBERT and (by invitation) DR. V. LEAF and DR. D. MUSGRAVE.

Carl W. Laymon, M.D., *President*

James R. Webster, M.D., *Secretary*

Jan. 18, 1950

Bowen's Disease. Presented by DR. MICHAEL H. EBERT and (by invitation) DR. V. LEAF and DR. S. BARSKY.

A 73 year old white man of German birth presents a group of crusted lesions over the left iliac crest.

About five years ago he first noticed a small lesion, which caused no subjective sensations. Three years ago it began to increase in size and to itch.

The patient has applied various remedies to the lesion, including ultraviolet ray treatment, without apparent effect on the lesion.

Physical examination reveals the following features: In an area the size of a silver quarter dollar there are three granulomatous lesions from 8 to 12 mm. in diameter covered with an adherent brownish crust. On removal of the crust, the two larger lesions are seen to be raised, moist and granulomatous. A fourth lesion was removed for histologic examination and is represented by a crusted scar.

The skin of the head, neck, upper part of the chest and hands presents the appearance of "farmer's skin" and has on it a few senile keratoses.

A biopsy of the lesion is presented and shows superficial epithelioma (squamous cell).

DISCUSSION

DR. OLIVER S. ORMSBY: I am quite interested in this dermatosis for the reason that it is very largely misunderstood. When Bowen first described the disease many years age he considered it purely a precancerous condition, but it was later demonstrated to be cancer from the beginning. The clinical picture shows a nodular keratotic lesion that looks like a serpiginous syphiloderm. It remains that way for many years before it breaks down. Since Bowen's report a number of cases have been described as being Bowen's disease that are not that at all. Most of them are multiple epitheliomas. In multiple epithelioma the lesion occurs as a scaling patch like psoriasis. This patch is surrounded by an epithelial margin, and it is really a basal cell epithelioma, while the lesion of Bowen's disease develops into a prickle cell tumor when it changes its type. Bowen's disease has been described as a lesion of the mucous membrane. It is, of course, impossible for it to be there. There have been a number of other cases described as Bowen's disease on account of their similarity. The case we see today is a typical example of true Bowen's disease. I think this is the first one that has been shown here in a good many years.

Chronic Discoid Lupus Erythematosus. Presented by DR. J. WEBSTER and DR. S. BLUEFARB and (by invitation) DR. D. MUSGRAVE.

Chronic Discoid Lupus Erythematosus with Parotid (?) Swelling. Presented by DR. STEPHEN ROTHMAN and DR. CALVIN J. DILLAHA (by invitation).

Acute Disseminated Lupus Erythematosus with Diffuse Alopecia in an 18 Year Old Negro Girl. Presented by DR. D. OMENS and (by invitation) DR. H. OMENS and DR. D. MUSGRAVE.

Lupus Erythematosus: Acute Dissemination Following Gold Therapy Successfully Treated with Aqueous Crysticillin.® Presented by DR. JAMES H. MITCHELL.

DISCUSSION OF CASES OF LUPUS ERYTHEMATOSUS

DR. A. L. WELSH, Cincinnati: I want to mention what I think seems to be a safe method of handling the subacute form of disseminated lupus erythematosus, disseminated discoid lupus erythematosus and chronic discoid lupus erythematosus. We have been using the alcohol of pantothenic acid and the calcium salt of pantothenic acid in high concentration, i. e., 2.5 to 3 Gm. daily. Both of these agents are well tolerated, and we have observed no reaction, except occasional nausea from the alcohol of pantothenic acid. The therapeutic effect is identical with each of these two agents and seems better than that of gold, bismuth and other heavy metal preparations. The improvement usually begins to take place after the third week and is regularly continuous.

In the long-standing chronic discoid type with lesions exhibiting heavy scarring and nodular borders, the response to these pantothenic acid preparations is much slower but eventually satisfactory.

In a few patients with acute disseminated lupus erythematosus treated with these drugs there has been practically no benefit at all. There have been no instances of exacerbation produced by these drugs. To date, no patient with subacute disseminated lupus erythematosus has had the condition change to the acute disseminated phase while on treatment with these drugs. These pantothenic acid preparations therefore, appear to be a much safer approach to the treatment of subacute disseminated lupus erythematosus.

DR. STEPHEN ROTHMAN: We did not intend to imply that the swelling in the parotid region in case 2 was a swelling of the parotid gland. On the contrary, the opinion of our ear, nose and throat department was that the gland and its duct are free. The cutaneous eruption preceded the swelling by ½ year. The patient has not yet been treated in our clinic.

DR. JAMES H. MITCHELL: I presented my case because I had previously found that in three exacerbations in one case the patient responded each time to intensive penicillin therapy. Whether it is a coincidence or not I do not know. This patient was near death with each exacerbation. There was a rapid disappearance of the acute symptoms that coincided with the time of penicillin therapy. I for one will keep that observation in mind on all occasions.

A Case for Diagnosis: Myxofibroma? Presented by DR. MICHAEL H. EBERT and (by invitation) DR. A. PEARL and DR. S. BARSKY.

J. S. is a 40 year old Polish-American laborer who presents a slowly growing tumor on the left index finger of 20 years' duration.

The lesion involves the entire dorsum of the distal phalanx of the left index finger up to the base of the nail. It is firm, nontender, slightly movable and of the color of the surrounding skin. The main lesion is dome-shaped, but there are several small satellites 2 mm. in diameter proximal to it. Two linear scars over the tumor represent operative sites of previously attempted removal of the mass.

Other physical examination and laboratory studies gave essentially normal results.

Two roentgenographic views of the left index finger showed no evidence of bone or joint pathologic changes.

DISCUSSION

DR. M. R. CARO: The diagnosis in this case should be made histologically, but unfortunately the pathologists did not agree. When Dr. Szymanski and I first examined the sections we made the diagnosis of myxofibroma. Another general pathologist diagnosed the condition as a cartilaginous tumor, probably malignant. Because of the presence of mucin in the tissue we feel the first diagnosis is correct. On clinical grounds, the lesion cannot be malignant for it has been there for 20 years. I think the lesion should be excised and subjected to further microscopic studies. I do not believe the finger should be amputated.

DR. MICHAEL H. EBERT: I thought this was an interesting tumor because of the satellite lesions. It did not look like an ordinary fibroma. It seems to me that in the few weeks we have had the patient under observation these satellites

A case for diagnosis: myxofibroma?

have increased in size and become yellower. I feel that not until the whole tumor is excised and a histologic study made can the final diagnosis be made. It is a unique case in my opinion.

NOTE.—Another biopsy taken later substantiated the diagnosis of myxofibroma.

Lupus Vulgaris Treated Successfully with Calciferol and Streptomycin.
Presented by DR. F. E. SENEAR and Staff.

A. B., a white woman 68 years old, had lupus vulgaris for many years. At admission two years ago, she presented a patch on the forehead about 2½ inches (6 cm.) in diameter. Her treatment at that time consisted in the administration of 50,000 units of calciferol and 1 Gm. of streptomycin daily. This was carried out for a period of six weeks. The patient has been observed since that time. During and for a time after the therapy, the lesions involuted, leaving thin scars.

The patient is presented now to show the continued good results following her treatment for six weeks two years ago.

DISCUSSION

DR. THEODORE CORNBLEET: It is noteworthy that even at the conclusion of treatment of lupus vulgaris with calciferol, when clinically all activity seems to be extinguished, one is surprised by how much remains to be seen histologically. Remembering this, one has little wonder at reactivations that occur in some cases even when no bacteria may be found in a thorough search.

DR. H. E. MICHELSON, Minneapolis: I believe it is the opinion of most observers who have used calciferol in the treatment of lupus vulgaris that the patient should be treated periodically over a period of three years even though a cure is apparent. That is, the patient should receive three to six weeks of treatment in the spring and fall after the active treatment is over. One of the remote dangers of the use of calciferol is hypertension. I have not seen that, but it is something to think about.

DR. EARL D. OSBORNE, Buffalo (by invitation): Those of you who attended the formal discussion groups at the Academy may recall that in my group the suggestion was made that we treat lupus vulgaris clinically by intradermal administration of streptomycin combined with procaine. Successful results were reported. It was recommended by two men from New York and one from the Middle West. They used 0.5 Gm. of streptomycin in 2 to 4 cc. of 2 per cent procaine hydrochloride and used that amount at one time by injection locally.

A Case for Diagnosis. Presented by DR. STEPHEN ROTHMAN, DR. DAVID COHEN and DR. LYDIA MARSHAK (by invitation).

S. S., a 56 year old white housewife, was first seen at the University of Chicago Clinics on Jan. 5, 1950, because of a widespread itching eruption which had first appeared on the dorsa of her hands 10 months ago and afterward on the extensor surfaces of her legs; a few weeks later "cold-sore"-like lesions appeared on lips and nose. The eruption rapidly became generalized. The mucous membranes of the mouth and genitalia have never been affected. Most of the lesions on the arms, legs and trunk present small grouped erythematous papules and papulovesicles. Older lesions, on the dorsa of the hands and on the face, show buttonlike nodules and large vegetative plaques with a soft papilliform surface.

The patient has taken a variety of drugs for several years, including phenobarbital, syntrogel® (a preparation containing aluminum hydroxide, calcium carbonate, magnesium peroxide and amprotropine phosphate in a mint-flavored demulcent base), acetylsalicylic acid and codeine. For a few weeks in April 1948 she took a medicine containing bromides. She denies taking bromo-seltzer® (a preparation containing acetanilid and sodium bromide) or laxatives.

The report on laboratory examinations was as follows: urinalysis—normal results; blood count—9,900 white blood cells, with 15 Gm. of hemoglobin, 59 polymorphonuclear cells, 9 eosinophils, 28 small lymphocytes and 4 monocytes. Kahn test, negative reaction. No bromides were found in the blood plasma, sweat or urine. Fluid from the minute vesicles grew hemolytic and nonhemolytic staphylococci on blood agar. Blister tops showed no growth on Sabouraud's medium. Coccidioidin and histoplasmin skin tests gave negative reactions. The oidiomycin skin test reaction was slightly positive. Repeated application of 30 per cent potassium bromide ointment on scarified skin showed no reaction. Reactions to patch tests with potassium iodide and potassium thiocyanate were negative.

A biopsy from a recent lesion on the left arm is presented: The section showed a parakeratotic purulent crust, pronounced acanthosis and intracellular and intercellular edema in the mucous layer. There were superficial intraepidermal vesicles filled with neutrophils and several microabscesses. The upper part of the corium showed edema. A dense infiltrate, consisting of numerous plasma cells, lymphocytes, eosinophils and a few neutrophils, was present in the upper part of the corium and in the midcorium. The infiltrate penetrated high up into the epidermis.

DISCUSSION

DR. LOUIS A. BRUNSTING, Rochester, Minn.: This eruption is an unusual one consisting of a widespread symmetrical exudative reaction on the trunk and extremities and a condition encircling the mouth which might be classified as dermatitis vegetans. Microscopic sections confirmed the clinical impression of a

form of eczema. In a recent report (Pyoderma Vegetans in Association with Chronic Ulcerative Colitis, ARCH. DERMAT. & SYPH. **60**:161-172 [August] 1949), Dr. Underwood and I emphasized the occurrence of a form of vegetating dermatitis in patients who had chronic ulcerative colitis and in one instance there was proved a definite relation to sensitivity to one of the sulfonamides. It is probable that some such allergic mechanism may be responsible for the peculiar picture on the skin in the patient presented here.

DR. M. R. CARO: I saw this patient several months ago. As I recall the case she had nothing at that time but a nummular eczema on the back of the hands. The picture today still suggests to me that she has nummular eczema plus dermatitis medicamentosa.

DR. PAUL A. O'LEARY, Rochester, Minn.: My interpretation of this woman's dermatosis is that it is a component of chronic infectious eczematoid dermatitis. The predominantly eczematoid features are distorted by the granulomatous-like lesions as noted, especially on the hands and forearms. The lesions about the mouth are quite similar to those we have seen in patients who are in the midst of an exacerbation of an ulcerative colitis. These lesions usually disappear as the bowel disease subsides, to recur, however, with subsequent flare-ups. I do not mean that this patient has colitis, but I do believe she is manifesting a rather bizarre cutaneous picture to a common bacterial agent.

DR. STEPHEN ROTHMAN: There is no history of ulcerative colitis, and we are unable to elicit a clearcut history of drug intake. If it is accepted that the basis of this condition is nummular eczema, we still are unable to explain the vegetations.

Atopic Dermatitis with Bilateral Cataracts. Presented by DR. F. E. SENEAR and Staff.

D. S., a 15 year old white schoolboy, was first seen by us on Jan. 11, 1950. He had a history of having had eczema on the face for six months when an infant. His skin remained clear until 3½ years ago, when an itchy eruption appeared on the cheeks, after which there was involvement of the extremities, neck and chest. Progressive impairment of vision started about six months ago. One and a half years ago the patient had asthma for several months.

Examination showed a decidedly erythematous weeping and crusted dermatitis on the face and neck. A lichenified crusted eruption was found on the flexures of the arms and legs and in the crural folds. There were many excoriations on all these areas. Opacities of each cornea were present. There was pupillary reaction to light.

DISCUSSION

DR. JOHN F. MADDEN, St. Paul: Cataracts which occur in atopic eczema often are unlike the usual senile cataract. They often are inoperable and result in permanent loss of vision, even in the very young. I have seen total blindness occur in atopic eczema in a patient 17 years of age.

DR. UDO J. WILE, Ann Arbor, Mich.: I should like to ask whether this patient had had any roentgen ray therapy for the eczema on the face.

DR. F. E. SENEAR: This patient had no roentgen ray treatment. That fact was the reason for showing this patient. We all recognized that cataract occurs in association with atopic dermatitis. I think that Dr. Brunsting has stated here before that not infrequently when patients have received radiotherapy for eczema and then have cataract medicolegal complications arise. The ophthalmologists can distinguish between cataract due to radiation and cataract due to atopic eczema. It is interesting in this case to recall the work of Dr. Jack Jones that was reported recently with regard to the tolerance of the eye tissues for radiation.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: Ophthalmologists are not always able to define cataracts according to the etiologic factors involved, and, even if they were, I am not sure that their word would carry much weight with members of a courtroom jury in deciding the true merits in the case of a patient who presents atopic dermatitis with cataracts and who has had more or less roentgen therapy to the face in times past.

Lipomelanotic Reticulosis (in Regression); Psoriasis. Presented by DR. FREDERICK R. SCHMIDT.

DISCUSSION

DR. PAUL A. O'LEARY, Rochester, Minn.: My discussion of this case will be confined to the diagnostic term employed and not to the patient. Pautrier suggested the term lipomelanotic reticulosis in describing the granulomatous hyperplasia with increase in melanin and fat deposits noted in the lymph nodes removed from patients with pruritic generalized dermatoses. These enlarged nodes, usually found in the inguinal or axillary regions, have been seen in patients with exfoliative dermatitis of arsenical and other origins, severe long-standing eczemas, generalized psoriasis and lichen planus. Most of these patients have increased skin pigmentation and severe pruritus. The term is suggestive of a new dermatologic entity, whereas it denotes merely the observation of a benign lymphadenopathy in patients with generalized dermatitis of one type or another. The general pathologists seem to have considerable difficulty interpreting these gland changes, especially if they are unfamiliar with the skin picture. Accordingly, lipomelanotic reticulosis is a confusing term which has been applied to a common complication of generalized eruptions of various causes. The glands disappear spontaneously with recession of the dermatoses, and there seems to be no need of perpetuating the term as an entity. The excision of a gland from a patient with a generalized eruption is not a simple procedure, as the gland invariably becomes infected and the period of hospitalization is thus increased.

DR. FREDERICK R. SCHMIDT: I agree with Dr. O'Leary 100 per cent. My reason for showing this case is that in spite of the fact that it has been repeatedly pointed out that the condition is a perfectly benign one associated with psoriasis, contact dermatitis, infantile eczema and other dermatoses, two pathologists who examined this slide at the hospital with which I am connected told me to look for an "obscure" melanoma. I also want to emphasize that this condition is reversible and that the skin may return to normal. The disorder does not have to end in lymphosarcoma, as Dr. Symmers originally expressed the belief.

Chrome Holes. Presented by DR. F. E. SENEAR and Staff.

S. G., a 44 year old white man, was first seen at the Dermatology Clinic of the University of Illinois Research and Educational Hospital on Jan. 16, 1950. For three months he had been employed as an electroplater, and in his work he had come into contact with chromium and chromium compounds. Three weeks ago he first acquired lesions on his hands and fingers. Only rubbing alcohol had been used locally.

On examination of the dorsa of the hands and fingers there may be observed numerous round, firm, tender, erythematous nodules, varying from 1 to 2 cm. in diameter. Most of these have a deep central ulcer which is necrotic or contains purulent material. Surrounding the central sinus there is a rim of whitish gray epidermis.

DISCUSSION

DR. EARL D. OSBORNE, Buffalo (by invitation): There is not much to be said that is not in the literature regarding chrome ulcers or chrome holes. Fortunately very little of this condition is seen at present compared to 20 or 25 years ago. Chrome plating of any type is now a closed process, so far as routine manufacturing processes are concerned. Chrome ulcers or chrome holes are seen in

experimental laboratories where new processes are being tried out. In chrome plating, as in other forms of metal plating, one is dealing with a metallic substance in a strong acid solution. The acid produces a superficial erosion, and there is penetration of the metallic substance into the deeper layers of the corium. Chemical examinations of excised chrome ulcers have shown chromium in appreciable quantities. Because of my interest in metallic substances deposited in the skin in the electroplating industry, I have been interested for many years in the retention in the skin of metallic substances, particularly chromium, after exposure to chrome paints and other sources of chromium. The same points apply to nickel. It can be demonstrated through skin washings and through chemical analyses of skin specimens that metallic substances remain in the skin for months or years, producing an eczematous process. This observation explains the chronicity and tendency to recurrence of many of these cases of dermatitis due to metallic sensitivity.

The usual site of chrome ulcers is the nasal septum, but it should be remembered that these lesions can occur on other parts of the body, particularly the genitalia. One of the worst cases I have seen was one involving the penis and scrotum, with extensive multiple ulceration. Chrome ulcers can also occur in the anal area.

Another point of importance when one considers exposure to chromium is the danger of the development of hypersensitivity after repeated exposure with resultant primary irritation, such as chrome ulceration.

Another point worthy of mention is that biopsy specimens removed from chrome ulcers have frequently in the past led to the diagnosis of epitheliomatous degeneration. In recent years I believe pathologists in general, and certainly dermatopathologists, are well aware of the difference between epitheliomatous degeneration and pseudoepitheliomatous degeneration in chronic ulcerations.

DR. L. F. WEBER: After chromium is deposited on abrasions of the skin, ulcers are likely to appear. The edges of the ulcers are thick and rounded and mildly reddened. The center of the ulcer is deep. Chrome ulcers have a tendency to persist for six or seven weeks. They usually leave a permanent scar. Chrome ulcers occasionally damage the eyelids and eyes. It has been my experience that chrome ulcers are often confused with malignant changes by the inexperienced industrial physician.

Solid Edema of the Eyelids; Streptococcic Dermatitis of the Ears.
Presented by DR. F. E. SENEAR and Staff.

A. B., a 51 year old white man, was first seen in the Dermatology Clinic of the University of Illinois on Jan. 12, 1950. One year previously he had noticed some swelling of the eyelids, beginning on the left side and later also involving the right. There had been four episodes of pronounced swelling, lasting three to four days, in which the eyes were closed by edema. Between these attacks the eyelids remained moderately swollen. For one month the ears, particularly the right, have been swollen and tender. There is no history of dental or sinus infection. Roentgenologic studies on Dec. 12, 1949, had shown evidence of minimal maxillary sinusitis. Blood pressure was recorded as 194/110. The bacteriologic report of cultures of the right ear was as follows: many Bacillus subtilis, few beta streptococci, a moderate number of diphtheroids, few Escherichia coli and few hemolytic Staphylococcus aureus.

Moderately puffy nonpitting edema with slight redness of the skin was noted about the right supraorbital and intraorbital areas. Less pronounced changes were noted about the left eye. The right ear was mildly edematous and red.

DISCUSSION

DR. PAUL A. O'LEARY, Rochester, Minn.: I believe this patient has solid edema of the face as a result of repeated attacks of erysipelas of the ear and face. The treatment in such situations is threefold: (1) the treatment of the

febrile attacks when they occur in the form of erysipelas or cellulitis or a streptococcic dermatitis, (2) attempts to prevent the recurrence of such attacks and (3) treatment of the edema.

The use of antibiotics usually controls the febrile sessions in three or four days. The prophylactic use of antibiotics, given during the interval between attacks, has supplanted the use of sulfonamides. They may be given for one or two days each week for a long period. In addition, a streptococcic bacterial vaccine may be given in increasing doses from 0.1 cc. up to 1.0 cc. at weekly intervals, and efforts should be directed toward treating the dermatitis of the ears, as in this patient, with antibiotics. It has been our experience that as the edema becomes greater the erysipelas attacks become more frequent. When these attacks occur on an extremity a para rubber bandage will minimize the edema and likewise reduce the frequency of the febrile attacks, although it will not completely eliminate them. Unfortunately, such mechanical measures are not applicable to facial edema. When the patient eventually acquires immune reactions and has not had an erysipelas or cellulitis attack for approximately a year and the edema persists, as it usually does, injections of boiling water into the edematous areas may be given. This operation is done with the patient under a general anesthetic and requires four to five days of hospitalization. The reactions are moderately severe for several days, and occasionally small superficial sloughs occur, which, however, heal readily. I repeat, for emphasis, that these hot water injections, which destroy the lymphatics, should be made only when the patient has not had an attack of erysipelas or cellulitis for approximately one year.

Dr. A. B. Loveman, Louisville, Ky.: We have under study now a man who has had edema of the upper eyelids for six to eight months. The erythema is negligible and appeared only after several months. We have had various investigations done and have found nothing except that the patient has subacute glaucoma. In St. Louis yesterday an English ophthalmologist described a non-inflammatory type of edema, limited to the upper eyelids, associated with glaucoma. The common denominator was allergy. It was felt that in such cases the glaucoma was due to allergy and the edema of the eyelids was likewise the result of the same allergen. In such cases, when the incriminating allergen was discovered and eliminated, both the glaucoma and the edema subsided. Desensitization injections were occasionally necessary.

Dr. Malcolm Spencer, Danville, Ill. (by invitation): Has anyone used hyaluronidase in such cases? Perhaps the spreading factor of this enzyme would offer some benefit. A patient with elephantiasis nostras involving the upper lip was treated recently in Philadelphia with hyaluronidase. Although the symptoms were of several years' duration, there was some improvement after four or five weekly subcutaneous injections. A final result of this case cannot be given.

Nevus Pigmentosus et Pilosus. Presented by Dr. James Webster and (by invitation) Dr. Francis Hetreed and Dr. Alfred B. Falk.

A. S., a white male aged 13 months, has had the presenting condition since birth. On examination, there is seen a large pigmented hairy nevus on the right side of the chest in the area of the right axilla. There are multiple similar dark growths of varied size located on the extremities and forehead.

Contemplated therapy is excision of the nevi on the forehead.

DISCUSSION

Dr. S. W. Becker: These examples of extensive nevi are not common. They are not entirely harmless because there have been several cases reported in the literature in which melanoma has originated even in childhood in such tumors. Then, too, associated with extensive pigmentation of the skin in many instances is increased pigmentation in the pia mater about the medulla. Mental symptoms

have resulted from benign and malignant melanoma originating in the nervous system. It is necessary to keep a sharp eye on these children to detect any malignant degeneration.

DR. F. R. SCHWARTZ: I know of a child with a similar nevus, treated with solid carbon dioxide, who died of malignant changes in the brain, especially about the pia mater.

DR. MARCUS R. CARO: I think that keeping a sharp eye on these cases, as suggested by Dr. Becker, is dangerous because by the time the visible changes do take place it is too late to do the patient much good. I think it is better in such a case to do plastic surgery early followed by a skin graft. I believe that the younger the child the better the chance of survival.

Keloidal Lesion of Suboccipital Area with Histological Picture of Myoblastoma. Presented by DR. H. RATTNER and DR. H. RODIN and (by invitation) DR. D. MUSGRAVE.

Von Recklinghausen's Disease with Involvement of Vertebrae and Long Bones. Presented by DR. H. RATTNER and DR. H. RODIN and (by invitation) DR. S. BARSKY.

A Case for Diagnosis: Blastomycosis of Sternal Region? Presented by DR. D. OMENS and (by invitation) DR. H. OMENS and DR. D. MUSGRAVE.

Blastomycosis of the Thigh and Groin with Clinical Picture Simulating Granuloma Inguinale. Presented by DR. D. OMENS and (by invitation) DR. H. OMENS and DR. S. BARSKY.

A Case for Diagnosis: Erythema Multiforme Bullosum? Pemphigus? Presented by DR. J. WEBSTER and DR. S. BLUEFARB and (by invitation) DR. D. MUSGRAVE.

Addison's Disease. Presented by DR. T. CORNBLEET and (by invitation) DR. D. COHEN and DR. S. BARSKY.

Rhinoscleroma. Presented by DR. D. OMENS and (by invitation) DR. H. OMENS and DR. S. BARSKY.

Nodular Tertiary Syphiloderm. Presented by DR. THEODORE CORNBLEET and (by invitation) DR. D. COHEN and DR. D. MUSGRAVE.

Hypotrichosis with Atrophy: Etiology (Woolly Hair Nevus? Hypothyroidism?). Presented by DR. SHELDON A. WALKER (by invitation).

A Case for Diagnosis: Lichen Ruber Moniliformis Kaposi? Mycosis Fungoides? Presented by DR. SAMUEL J. ZAKON, DR. ROYAL E. IHRKE and DR. AARON L. GOLDBERG (by invitation).

Favus in Five American-Born Siblings. Presented by DR. STEPHEN ROTHMAN and DR. SHELDON A. WALKER (by invitation).

News and Comment

GENERAL NEWS

Specialists Certified by the American Board of Dermatology and Syphilology.—At the last meeting of the American Board of Dermatology and Syphilology, held in Detroit, October 20 to 22, 1950, the following candidates were found proficient and are now certified specialists: Jack J. Albom, New Haven, Conn.; Samuel D. Allison, Honolulu, T. H.; Harry Arons, Newark, N. J.; Sam C. Atkinson Jr., Summit, N. J.; John H. Barthell, Lincoln, Neb.; Sigmund J. Clayman, New York; Hugh M. Crumay, Philadelphia; Frank X. Dwyer, Kansas City, Mo.; George Gaethe, New Orleans; Calvin B. Galloway, Camp Lejeune, N. C.; Frederick C. Grieshaber, New Orleans; Edward F. Gudgel, Kenmore, N. Y.; Arthur E. Gulick, Detroit; Milton H. Gustafson, Muncie, Ind.; Milton E. Helman, Chelsea, Mass.; Edwin N. Hesbacher, Richmond, Va.; Edwin L. Higgins, Covington, Ky.; Elmer M. Hill, Minneapolis; Frank C. Hoak, Buffalo; Sidney Hoffman, Brooklyn; Samuel Holtzman, Chicago; Wilbur B. Hurlbut, New York; Frank D. Jennings Jr., Brooklyn; H. Fred Johnson, Amarillo, Texas; Henry W. Jolly Jr., Baton Rouge, La.; Carl K. Kaufman, Las Vegas, Nev.; John R. King, Grosse Pointe, Mich.; William E. Laur, Amarillo, Texas; Roy W. Leeper, Boston; George D. McAfee, Cincinnati; Leonard Meltzer, Houston, Texas; Coleman Mopper, Detroit; Isaac M. Paley, South Norwalk, Conn.; William N. Piper Jr., Washington, D. C.; George Prazak, El Paso, Texas; Everett C. Ravits, Hackensack, N. J.; J. Sidney Rice, Fort Lewis, Wash.; William Rosensweig, Wilkes-Barre, Pa.; John J. Sevenants, La Crosse, Wis.; Meyer H. Slatkin, Brooklyn; Robert G. Thompson, Washington, D. C.; Arthur J. Tronstein, Newark, Ohio; Manly Utterback, Ogden, Utah; John D. Walters, Bethesda, Md.; Abraham I. Weidman, Brooklyn; Raymond M. Williams, Denver, and Meyer Yanowitz, Miami, Fla.

The dermatologists in the following list also passed the examination and will become certified specialists after they have completed five years in the specialty: John W. Baird, Memphis, Tenn.; Sidney Barsky, Maywood, Ill.; Patrick G. Butler, San Francisco; James W. S. Calvert, New York; Vincent J. Cirincione, New York; Byron Clyman, Norristown, Pa.; Dale D. Doherty, Corona, N. Y.; John W. Doughtery, New York; Joseph A. Elliott Jr., Charlotte, N. C.; Bruce M. Esplin, Miami, Fla.; William S. Gibson, Pittsburgh; Jack W. Graffin, Los Angeles, Calif.; Leonard C. Greenfield, San Diego, Calif.; Marshall Beck Guthrie, Phoenixville, Pa.; Frederick V. Hauser, Chicago; David L. Hearin, Atlanta, Ga.; Grace P. Kerby, Durham, N. C.; William T. Kruse, East Grand Rapids, Mich.; Myron H. Kulwin, Champaign, Ill.; Owen G. Miller, Salem, Ore.; James L. Mims, Spartanburg, S. C.; John C. Murphy, Albuquerque, N. M.; Matthew A. Olivo, Camden, N. J.; Leo Orris, New York; Richard S. Refowich, Bethlehem, Pa.; Bernard L. Rosenberg, New York; Donald Rosman, Los Angeles; Harvey C. Roys Jr., Seattle; Joseph S. Shapiro, Paterson, N. J.; Harry Shatin, Bronx, N. Y.; Benneth L. Snider, Binghamton, N. Y.; Margaret A. Storkan, St. Paul; David R. Taylor, Reedley, Calif.; John R. Tobey, Newark, N. J.; Harold E. Usndek, Detroit, and Sydnor T. Withers, Great Lakes, Ill.

SPECIAL NOTICE

For the general information of indexers, catalogers and library personnel with reference to the listing of the new title of this journal, we advise that the *Quarterly Cumulative Index Medicus* policy be followed. The *Quarterly Cumulative Index Medicus* with its volume 49 (January-June 1951) will list this journal under the new title, so that the letters A. M. A. will be included as an integral part of the title. For the completion of volume 48 (July-December 1950) the *Quarterly Cumulative Index Medicus* will continue to use the old title, without adding the designation A. M. A.

Book Reviews

Non-Gonococcal Urethritis, Including the Genital Manifestations of Local Systemic Diseases and Infestations of the Urinary Tract with Protozoa, Metazoa and Fungi. By A. H. Harkness, M.R.C.S. (Eng.), L.R.C.P. (Lond.). Price, $10. Pp. 424, with 167 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves, Baltimore 2, 1950.

As the title would indicate, this book by an English author is primarily of interest to the urologist. Of the 31 chapters, two are of direct interest to dermatologists. These chapters are concerned with Reiter's disease and keratodermia blennorrhagica.

According to the author's definition, "Reiter's disease (its etiology is unknown) is characterized by a clinical syndrome consisting of a primary abacterial urethritis of venereal origin, bilateral conjunctivitis, polyarthritis, frequently balanitis, and sometimes keratodermia blennorrhagica; cardiac and other manifestations have also been described."

A thorough discussion of this syndrome is given, including history of its recognition; clinical observations in over 100 cases, illustrated by two photographs and numerous reproductions of roentgenograms; differential diagnosis; treatment, and a summary of theories and facts bearing on the etiology of the disease. The author has demonstrated (as have other recent workers) the presence of pleuropneumonia-like organisms in urethral cultures in a high percentage of cases. He also has found a few cases in which inclusion bodies suggesting a virus origin were found in cells scraped from the urethral mucosa. His belief that the disease is venereal may be challenged by some in this country.

Keratodermia blennorrhagica is discussed under the heading of Reiter's disease, the author feeling that the former condition is a blood-borne manifestation of nonbacterial urethritis and that its occurrence in cases of gonococcic urethritis is the result of a mixed infection, the gonococcus playing no part in the appearance of the eruption. Several drawings in color and one photograph illustrate the clinical manifestations. The histopathology, etiology and differential diagnosis are discussed at length.

Brief sections elsewhere in the book discuss the urethritis sometimes found in association with various systemic and skin diseases, including syphilis, leprosy, erythema multiforme, Behcet's syndrome, papulonecrotic tuberculid, lymphogranuloma venereum, granuloma inguinale and chancroid.

The information on the two diseases discussed at length above considerably surpasses that available in current textbooks of dermatology and far exceeds the meager paragraph allotted to Reiter's disease in most American textbooks of medicine.

For the two chapters on Reiter's disease and keratodermia blennorrhagica alone the book can be highly recommended as an excellent reference book for dermatologists.

Lehrbuch der Haut- und Geschlechtskrankheiten. By Georg Alexander Rost, Emeritus Professor Ordinary of Dermatology and Directing Physician of the Dermatological Clinic of the Berlin-Spandau City Hospital. Second edition. Price, 12 Reichsmark. Pp. 162. Springer-Verlag, Jebensstrasse 1, Berlin-Charlottenburg 2, 1948.

This is a small book of 162 pages, covering the entire field of clinical dermatology and venereology. It is well indexed and includes a two page formulary. The subject matter is well organized and well presented and covers most of the important dermatological entities. In order for there to be such a wide coverage the individual dermatoses are discussed only briefly and are identified by their most outstanding features. The book is, therefore, of only limited value to English-speaking dermatologists.

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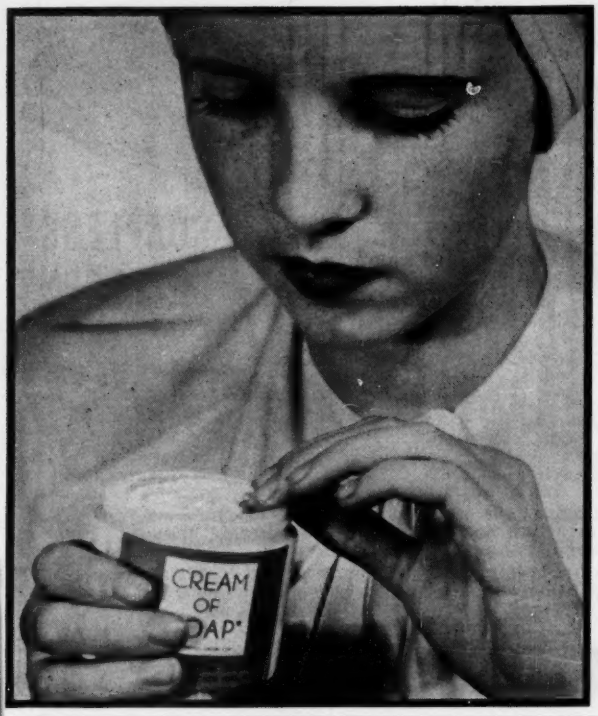

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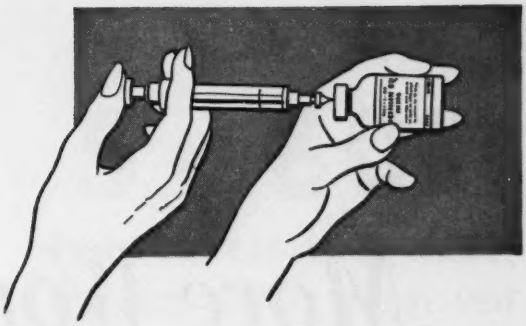

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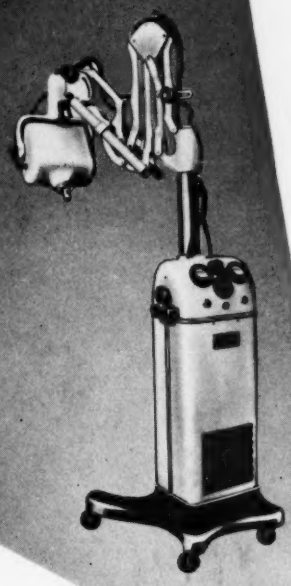

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